ACP | MKSAP® 19

Medical Knowledge Self-Assessment Program®

Nephrology

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Nephrology

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The learning objectives of MKSAP 19 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve clinical management decisions that affect patient safety and quality of care
- Determine when to refer patients for care by medical subspecialists, surgeons, and other members of the health care team
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internal medicine specialists, including primary care physicians and hospitalists
- Internal medicine subspecialists who desire to remain up to date in internal medicine
- Residents preparing for the ABIM Internal Medicine Certification Examination
- Physicians engaged in the ABIM Maintenance of Certification Longitudinal Assessment Option, preparing for the ABIM Internal Medicine Maintenance of Certification Examination, or engaged with the ABIM Focused Practice in Hospital Medicine program

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Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon [HVC].

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Nephrology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 19 in several important ways. MKSAP 19 includes HVC-identified key points in the text, HVC-focused multiple-choice questions, and, in MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Nephrology section of MKSAP 19.

- The random (spot) urine protein-creatinine ratio and albumin-creatinine ratio correlate with 24-hour urine collections and are sufficiently accurate for screening and monitoring proteinuria.
- There is no need to monitor urine protein excretion in patients who are taking an ACE inhibitor or angiotensin receptor blocker.
- In the treatment of diabetic kidney disease, combining any two renin-angiotensin system drug classes (ACE inhibitors, angiotensin receptor blockers, or direct renin inhibitors) is not recommended, as side effects are increased and there is no additional clinical benefit.
- Urinalysis should not be used for urothelial cancer screening in asymptomatic adults.
- CT urography is preferred to MRI as the diagnostic test of choice for patients with unexplained hematuria (see Item 59).
- In the treatment of symptomatic hyponatremia, simultaneous administration of desmopressin with 3% saline infusion results in a more predictable and safer increase in serum sodium (see Item 90).
- The treatment of isovolemic hypernatremia is water, preferably orally or by nasogastric tube if the patient is incapable of drinking, rather than intravenously (see Item 60).
- Baseline echocardiography is not routinely recommended but should be performed if examination or ECG suggest cardiac hypertrophy or to evaluate the need for therapy in patients with white coat hypertension.
- Adults with stage 1 hypertension who have an estimated 10-year atherosclerotic cardiovascular disease event risk of <10% should be managed initially with nonpharmacologic therapy (see Item 52).
- Treatment of chronic hypertension (<160/110 mm Hg) during pregnancy is not associated with improved fetal outcomes (see Item 13).
- In most patients with renal artery stenosis, the primary therapeutic intervention is medical management (see Item 18).
- For patients with suspected renal artery fibromuscular dysplasia, CT angiography is preferred to MRI as the initial imaging modality of choice (see Item 48).
- In younger patients with IgA nephropathy, recurrent hematuria in the absence of proteinuria usually portends a benign clinical course and treatment is conservative (see Item 41).
- Serologic testing for anti-phospholipase A2 receptor antibodies in patients with suspected primary membranous nephropathy can eliminate the need for kidney biopsy in patients with preserved kidney function and no evidence of secondary causes (see Item 75).
- Primary membranous nephropathy is typically treated with conservative therapy before initiating immunosuppression for patients with persistent nephrotic-range proteinuria to allow for spontaneous remission, which occurs in approximately 30% of patients.
- Contrast-associated nephropathy prophylaxis is not indicated for patients with a stable estimated glomerular filtration rate ≥45 mL/min/1.73 m^2 (see Item 2).
- There is no proven benefit to early administration of renal replacement therapy versus timing based on usual clinical criteria in critically ill patients or those with sepsis.
- In the diagnosis of nephrolithiasis, ultrasonography does not expose patients to radiation, has a lower cost compared with CT, and is the preferred modality during pregnancy (see Item 69).
- The most effective treatment to facilitate the passage of uric acid stones is urinary alkalinization with potassium citrate (see Item 54).
- Use of potassium binders in patients with chronic kidney disease may allow continuation of essential medications,

such as inhibitors of the renin-angiotensin system (see Item 106).

- Erythropoiesis-stimulating agents should not be used for most patients with chronic kidney disease and hemoglobin >11 g/dL (110 g/L) because of an increased risk for serious cardiovascular events and stroke.
- For older patients with end-stage kidney disease and those who are not transplant candidates, screening for renal cell carcinoma is not recommended, even in the presence of known acquired cystic kidney disease (see Item 5).
- For eligible patients, kidney transplantation is the preferred treatment for end-stage kidney disease because of improved mortality and quality of life and decreased health care costs.
- Patients who receive preparatory renal replacement therapy (RRT) education before they are diagnosed with end-stage kidney disease are more likely to select a home modality for RRT, be listed for a kidney transplant, or receive a preemptive kidney transplant and may have a mortality benefit compared with patients who do not receive similar education (see Item 46).
- Non-dialytic palliative therapy is a reasonable option for older patients with end-stage kidney disease and multiple comorbidities, with treatment focusing on symptom management and quality of life.

Nephrology

Clinical Evaluation of Kidney Function

Assessment of Kidney Function

The kidney selectively removes waste while retaining needed substrate, maintains fluid and electrolyte homeostasis, and regulates blood pH. Glomerular filtration rate (GFR) measures total nephron filtration of blood and correlates closely with toxin removal and overall kidney function. Early loss of kidney function is difficult to detect because compensation through hypertrophy and hyperfiltration preserve GFR despite nephron loss. Other markers of disordered glomerular function, such as proteinuria and hematuria, are also indicators of kidney disease that may precede any evidence of reduced filtration.

Biochemical Markers of Kidney Function

Although numerous methods for estimating kidney function are available (**Table 1**), serum creatinine and serum cystatin C are the primary biomarkers used to estimate GFR.

Serum Creatinine

Serum creatinine is the most extensively used measure of kidney function. Creatinine is freely filtered by the glomerulus and is also secreted into the urine by the proximal tubule. The relationship of serum creatinine to GFR is nonlinear; significant losses in kidney function at higher GFR may be masked by only small changes in serum creatinine, whereas small filtration changes at lower GFR are associated with large fluctuations in serum creatinine (**Figure 1**). The contribution of tubular secretion as a proportion of total creatinine excretion increases as GFR declines. Therefore, when urinary creatinine clearance is used to estimate GFR, secreted creatinine will contribute to overestimation of true GFR. With complete loss of kidney function (anuria), serum creatinine may increase by up to 1.0 mg/dL (88.4 µmol/L) per day in patients with average muscle mass.

Creatinine is a metabolite of creatine, which is mostly present in skeletal muscle. Persons with higher muscle mass (such as younger people, men, and Black persons) have a higher serum creatinine compared with less muscular persons with the same GFR. Loss of muscle mass seen with aging, muscle wasting, malnutrition, or amputation will result in lower serum creatinine despite stable GFR. In persons with decreased muscle mass, serum creatinine therefore tends to overestimate the GFR.

Some medications reduce proximal tubule secretion of creatinine. These drugs include cimetidine, trimethoprim, cobicistat, dolutegravir, and bictegravir and result in elevated serum creatinine despite stable GFR.

Serum Cystatin C

Cystatin C is produced by all nucleated cells, freely filtered by glomeruli, and catabolized by tubules. Compared with serum creatinine, serum cystatin C levels are less affected by age, sex, or muscle mass, but may be increased by acute disease (such as malignancy, hyperthyroidism, inflammation, or HIV infection). Changes in serum cystatin C may identify small decreases in kidney function better than serum creatinine. Formulas using cystatin C to estimate GFR are helpful for patients in whom creatinine-based GFR may be inaccurate (such as in cases of drug-induced reduction of creatinine secretion described earlier, or in those with reduced or increased muscle mass).

Blood Urea Nitrogen

Blood urea nitrogen (BUN) is a product of protein metabolism. Levels increase with reduced GFR and with increased urea reabsorption caused by renal hypoperfusion. BUN is also affected by protein intake and catabolic rate. Lower levels are noted in starvation and in patients with liver disease. BUN will increase with glucocorticoids, hemorrhage, or trauma. BUN may be useful in detecting renal hypoperfusion when elevation of BUN from increased reabsorption is disproportionate to the rise in serum creatinine level.

Estimation of Glomerular Filtration Rate

Creatinine-based formulas are used to estimate GFR by adjusting for factors that affect serum creatinine and creatinine clearance. These formulas take into account the effects of age, race, sex, and muscle mass (estimated by weight) on serum creatinine levels (see Table 1).

The Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration creatinine equation is the most widely used method for estimating GFR and is the most accurate equation for most persons, particularly in older persons and those with a GFR >60 mL/min/1.73 m^2. A newer CKD-EPI creatinine-cystatin C equation is the most accurate, but requires cystatin C data and works optimally in patients of normal body mass.

The Modification of Diet in Renal Disease (MDRD) study equation does not accurately estimate high GFRs. It performs similarly to the CKD-EPI equation at GFRs <60 mL/min/1.73 m^2. Clinical laboratories that use the MDRD do not report GFRs >60 mL/min/1.73 m^2; therefore, physicians may not be aware of the presence of kidney disease. In this context, an

TABLE 1. Methods for Estimating Kidney Function

Method	Applications	Considerations
Serum Creatinine		
	Most frequently used assessment of kidney function	Nonlinear relationship with GFR Nonkidney effects on blood levels (muscle mass, drugs affecting tubular secretion)
Serum Cystatin C		
	More accurate in older persons and patients with cirrhosis due to low muscle mass More accurate in those with an increase in muscle mass Sensitive to mild changes in GFR	Levels are affected by diabetes mellitus, hyperthyroidism, inflammation, glucocorticoid use, malignancy, HIV infection
Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration Equation		
CKD-EPI Creatinine		
Variables include serum creatinine, age, race, and gender	More accurate than MDRD and CGE equations in older persons and in those with GFR >60 mL/min/1.73 m^2	Preferred formula for calculating creatinine-based GFR Self-reported race may reduce reliability of this and all CKD-EPI equations
CKD-EPI Cystatin C		
Variables include serum cystatin C, age, and gender	Can be used as confirmatory test for CKD May be more accurate than creatinine-based equation in those with muscle wasting, chronic illness, or high muscle mass	Helpful in estimating GFR in those taking drugs that affect creatinine secretion (e.g., cobicistat, dolutegravir, bictegravir, trimethoprim, and cimetidine)
CKD-EPI Creatinine-Cystatin C		
Equation uses same variables as CKD-EPI creatinine but different exponents and includes serum cystatin C	Creatinine-cystatin C combination provides the most accurate eGFR in most patient populations	–
Modification of Diet in Renal Disease (MDRD) Study Equation		
Variables include serum creatinine, age, race, and gender	Similar accuracy as CKD-EPI when eGFR is 15-60 mL/min/1.73 m^2	Most accurate when eGFR is 15-60 mL/min/1.73 m^2 Underestimates GFR when GFR >60 mL/min/1.73 m^2
Creatinine Clearance (CrCl)		
Variables include serum and urine creatinine and 24-hour urine volume	Useful in pregnancy, extremes of age and weight, amputees, malnourished and cirrhotic patients (situations where creatinine is low, so CKD-EPI and MDRD will overestimate GFR)	Overestimates GFR 10%-20% Overestimation worsens with lower GFR (due to increased ratio of creatinine secretion to filtration) Over- or undercollection limits accuracy
Cockcroft-Gault Equation (CGE)		
Variables include serum creatinine, body weight, age, and gender	Improved accuracy when age is <65 years	Most accurate when eGFR is 15-60 mL/min/1.73 m^2 Underestimates GFR in obesity Overestimates GFR when BMI <25
Radionuclide Kidney Clearance Scanning		
Iothalamate GFR scan or diethylenetriamine pentaacetic acid (DTPA) GFR scan	Useful in kidney donor evaluation if eGFR is borderline for donation or other times when accurate prediction is essential DTPA can be used for determination of relative (differential) function of each kidney (e.g., prenephrectomy)	Most precise method; expensive; exposure to radiation

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate.

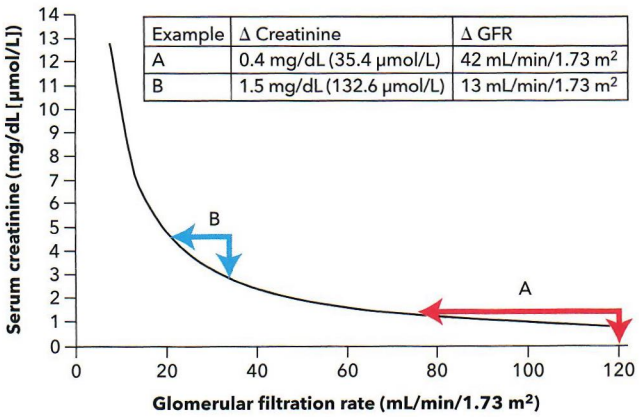


FIGURE 1. The relationship between serum creatinine and glomerular filtration rate (GFR). Example A illustrates that a small increase in the serum creatinine level in the reference range (in this case, 0.8-1.2 mg/dL [70.7-106.1 µmol/L]) reflects a relatively large change in GFR (120 to 78 mL/min/1.73 m^2). Example B illustrates that a relatively greater increase in the serum creatinine level (in the high range of 3.0-4.5 mg/dL [265.2-398 µmol/L]) reflects a proportionately smaller change in GFR (35 to 22 mL/min/1.73 m^2).

increasing serum creatinine level, proteinuria, or other urine abnormalities should alert the clinician to the presence of kidney disease.

When using CKD-EPI or MDRD to calculate drug dosages requiring adjustment for GFR, estimated GFR (eGFR) should be multiplied by body surface area (BSA)/1.73 m^2, particularly in persons with very high or very low BSA.

The Cockcroft-Gault equation (CGE) is the least accurate method. However, it remains in use for drug dosing because it was used in pharmacokinetic studies for most medications.

Creatinine clearance obtained by using 24-hour urine collection is a better measure of GFR than serum creatinine, but it is not recommended for routine estimation of GFR because it is affected by the accuracy of collection and by tubular creatinine secretion.

Radionuclide imaging provides the most accurate measurement of GFR and is the gold standard in research. It is useful for accurate determination of GFR during evaluation of kidney donors, evaluation of recipients for other organs, and assessment of the differential GFR of each kidney before nephrectomy.

KEY POINTS

- Serum creatinine changes nonlinearly with glomerular filtration rate (GFR), and significant losses in kidney function at higher GFR may cause only small changes in serum creatinine.
- The Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration creatinine equation is the most widely used equation to estimate glomerular filtration rate (GFR); it is the most accurate equation for most persons, particularly in older persons and those with a GFR >60 mL/min/1.73 m^2.

Interpretation of the Urinalysis

Urine dipstick and urine microscopy are indicated in the evaluation of both acute and chronic kidney disease (**Table 2**). Analysis is best performed on a fresh specimen within 30 to 60 minutes of voiding. Midstream collection is preferred with a clean catch in women and uncircumcised men.

Urine Dipstick

See Table 2 for details on urine dipstick.

Specific Gravity

Specific gravity measures hydration status and reflects the kidney's ability to concentrate urine.

pH

Low urine pH may occur in persons eating high-protein diets. Alkaline urine (pH ≥7.0) can occur in strict vegetarians and in persons with infections caused by urea-splitting organisms. Urine pH may be inappropriately high in some forms of renal tubular acidosis (type 1 distal) but may be appropriately low in others (type 4 distal).

Blood

Dipsticks detect peroxidase activity of blood and free heme pigments (hemoglobin and myoglobin). Three or more erythrocytes result in a positive test (1+ blood). A positive test in the absence of erythrocytes in the urine sediment may indicate myoglobinuria (due to rhabdomyolysis) or hemoglobinuria (due to intravascular hemolysis following transfusion, or shear stress related to mechanical heart valve and perivalvular leak). False-positive tests may occur with other substances with peroxidase activity, including peroxidase-expressing bacteria and drugs such as chloroquine. Ascorbic acid can cause a false-negative result. Medications (rifampin, phenytoin) or food (beets) can cause heme-negative, red-colored urine.

Protein

Although various proteins may be present in urine, the dipstick preferentially detects albumin. Because dipsticks are dependent on urine concentration, false negatives may result from dilute urine and false positives from highly concentrated urine. Because moderately increased albuminuria (formerly known as microalbuminuria) may go undetected by dipstick, direct quantification of albuminuria and/or proteinuria using a random (spot) protein-creatinine ratio or albumin-creatinine ratio or a 24-hour urine collection is required in high-risk patients. False-positive tests can occur with highly alkaline urine specimens.

Glucose

Glucosuria typically occurs when plasma glucose exceeds 180 mg/dL (10.0 mmol/L). Glucosuria in the absence of hyperglycemia suggests proximal tubular dysfunction, as seen with myeloma or exposure to drugs (such as tenofovir disoproxil

TABLE 2. Findings on Urinalysis

	Normal Range	Comments
Dipstick		
Specific gravity	1.005-1.030	Low: dilute urine from excess hydration; impaired urine concentration (diabetes insipidus; sickle cell nephropathy; acute tubular injury)
		High: volume depletion; renal hypoperfusion; excretion of hypertonic solute (glycosuria; contrast dye)
pH	5.0-6.5	Low/acidic: high-protein diets; type 4 distal RTA; some type 2 proximal RTA; increases risk for uric acid and cystine calculi
		High/alkaline: urease-splitting organisms (most commonly *Proteus* species; other potential organisms include *Escherichia coli* and *Pseudomonas*, *Klebsiella*, and some staphylococcal species); low acid ingestion; type 1 distal RTA; some type 2 RTA; increases risk for struvite and calcium phosphate calculi
Blood/heme pigments	None	Positive: hemoglobin or myoglobin; absence of erythrocytes suggests myoglobinuria or intravascular hemolysis
		False positive: alkaline urine (pH >9)
Protein	None to trace	Dipsticks primarily detect albumin; concentration dependent (trace positive can be normal in a concentrated specimen); not sufficiently sensitive to detect moderately increased albuminuria
		Graded as trace (10-30 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), 4+ (>1000 mg/dL)
Glucose	None	Positive: plasma glucose exceeds ~180 mg/dL (10.0 mmol/L); proximal tubule defect (Fanconi syndrome); pregnancy (lower excretion threshold)
Ketones	None	Detects acetone and acetoacetic acid, not β-hydroxybutyrate
		Positive: diabetic ketoacidosis; starvation; vomiting; pregnancy
Leukocyte esterase	None	Enzyme found in leukocytes; indicates pyuria (possibly from UTI); positive test requires ≥5 leukocytes/hpf
Nitrites	None	Produced by gram-negative bacteria from nitrates
		Positive: suggests UTI
		Negative: does not rule out UTI (specific but not sensitive)
Microscopic		
Erythrocytes	0-2/hpf	Urine microscopy should be performed to evaluate erythrocyte morphology
Leukocytes	0-4/hpf	The presence of any leukocytes may be abnormal depending on clinical circumstances
Squamous epithelial cells	<15/hpf	Increased epithelial cells indicates contamination
Casts	None or hyaline	Hyaline casts: indicative of poor kidney perfusion
		Granular casts: acute tubular necrosis
		Erythrocyte casts: glomerular bleeding/glomerulonephritis
		Leukocyte casts: infection; acute interstitial nephritis
Crystals (see Table 3)	None	Most common: calcium oxalate, calcium phosphate, uric acid, and struvite

RTA = renal tubular acidosis; UTI = urinary tract infection.

fumarate). Sodium-glucose cotransporter-2 inhibitors, such as empagliflozin and canagliflozin, cause glucosuria by preventing reabsorption of glucose. Glucosuria may be present in normal pregnancy due to changes in tubular threshold for glucose reabsorption.

Ketones

Ketonuria most commonly occurs in starvation, diabetic ketoacidosis, and alcoholic ketoacidosis. Urine ketones are also seen in salicylate toxicity and isopropyl alcohol poisoning. Urine dipstick detects acetone and acetoacetate but not β-hydroxybutyrate; therefore, in diabetic ketoacidosis and alcoholic ketoacidosis where β-hydroxybutyrate is the primary ketone, the dipstick underestimates ketone excretion. False-positive tests may occur with drugs containing sulfhydryl groups, such as captopril.

Leukocyte Esterase and Nitrites

Leukocyte esterase is an enzyme present in leukocytes. A positive test suggests pyuria (≥5 leukocytes/hpf).

A positive nitrite test signifies the presence of gram-negative bacteria (*Escherichia coli*; *Klebsiella*, *Enterobacter*,

Citrobacter, and *Proteus* species) capable of converting urine nitrates into nitrites. The test is falsely negative if there is inadequate contact time for urine nitrates with the bacteria. The nitrite test is negative in urinary tract infection (UTI) caused by nonconverting organisms (*Enterococcus*, *Staphylococcus*, *Streptococcus*, or *Haemophilus* species).

The presence of both leukocyte esterase and nitrites on urine dipstick is highly predictive of a UTI; conversely, the absence of both has a high negative predictive value for a UTI.

Bilirubin

Bilirubin should be absent from the urine when serum levels are normal. Conjugated, water-soluble bilirubin is excreted in the urine in severe liver disease or obstructive hepatobiliary disease.

Urobilinogen

Gut bacteria produce urobilinogen through metabolism of bilirubin. Urobilinogen is then absorbed via portal circulation and excreted in urine. Increased urobilinogen is associated with hemolytic anemia or parenchymal liver disease. Decreased levels are seen with severe cholestasis and obstructive disease.

KEY POINTS

- Because moderately increased albuminuria may go undetected by dipstick, direct quantification using a random (spot) protein-creatinine ratio or albumin-creatinine ratio or a 24-hour urine collection is required in high-risk patients.
- The presence of both leukocyte esterase and nitrites on urine dipstick is highly predictive of a urinary tract infection (UTI); conversely, the absence of both has a high negative predictive value for a UTI.

Urine Microscopy

Microscopic assessment of urine sediment (**Figure 2**) is indicated for patients with abnormalities on dipstick and in those with acute kidney injury, newly diagnosed chronic kidney disease, or suspected glomerulonephritis. See Table 2 for details on urine microscopy.

Erythrocytes

Erythrocyte morphology may indicate their origin (see Figure 2). Isomorphic erythrocytes (round and of consistent size) suggest a nonglomerular origin as a result of infection, mass, cyst, or stone. Dysmorphic erythrocytes, which are fragmented erythrocytes with significant variability, suggest glomerular bleeding. Acanthocytes, a form of dysmorphic erythrocytes characterized by vesicle-shaped protrusions, are most suggestive of a glomerular source of bleeding. Dysmorphic erythrocytes should result in prompt evaluation for glomerulonephritis (**Figure 3**). See Clinical Evaluation of Hematuria for more information.

Leukocytes

The presence of ≥5 leukocytes in the urine sediment indicates pyuria, which is most commonly caused by a UTI. Sterile pyuria is the presence of urine leukocytes in the setting of negative urine culture; common causes include vaginitis and cervicitis in women, prostatitis in men, acute interstitial nephritis (AIN), kidney stones, kidney transplant rejection, and, less commonly, UTIs due to organisms that do not grow by standard culture techniques (*Chlamydia* species, *Mycobacterium tuberculosis*, *Ureaplasma urealyticum*). The absence of leukocytes does not rule out AIN.

Eosinophils

Urine eosinophils suggest interstitial nephritis, atheroembolic disease, glomerulonephritis, small-vessel vasculitis, UTI, prostatic disease, or parasitic infections. Poor sensitivity and specificity limit the utility of urine eosinophils in the diagnosis of interstitial nephritis.

Epithelial Cells

Renal tubular, transitional, and squamous epithelial cells may be seen on urinalysis (see Figure 2). Renal tubular epithelial cells are round with central nuclei and are 1.5 to 3 times larger than leukocytes. Their presence in the context of granular casts suggests acute tubular necrosis. Transitional epithelial cells are slightly larger than renal tubular epithelial cells and may be binucleate; they originate anywhere from the renal pelvis to the proximal urethra. Squamous epithelial cells are the largest epithelial cells, and are flat and irregular with small central nuclei; they are derived from the distal urethra or external genitalia, and their presence in large numbers (>15/hpf) denotes contamination by genital secretions.

Casts

The backbone of all urine casts is a matrix composed of Tamm-Horsfall protein (uromodulin). These cylindrical casts form in the distal tubular lumen. Any cells or debris in casts must be present in the tubule at the time of cast formation, having originated from a more proximal part of the nephron. Erythrocyte casts are highly suggestive of glomerulonephritis. Leukocyte casts may be present in AIN and infections (pyelonephritis). Pigmented or granular (muddy brown) casts contain tubular cell debris (**Figure 4**) and may be present in acute tubular necrosis. The severity of acute kidney injury correlates with the number of casts and presence of renal tubular epithelial cells.

Crystals

Crystalluria results from the supersaturation of solutes in concentrated urine. These solutes are derived from metabolic disorders, inherited diseases, drugs, or toxins. **Table 3** describes features of common crystals. Certain drugs can crystallize in concentrated urine and when used in high doses, including sulfadiazine, sulfamethoxazole, intravenous acyclovir, methotrexate, and atazanavir.

(*Text continued on page 8*)

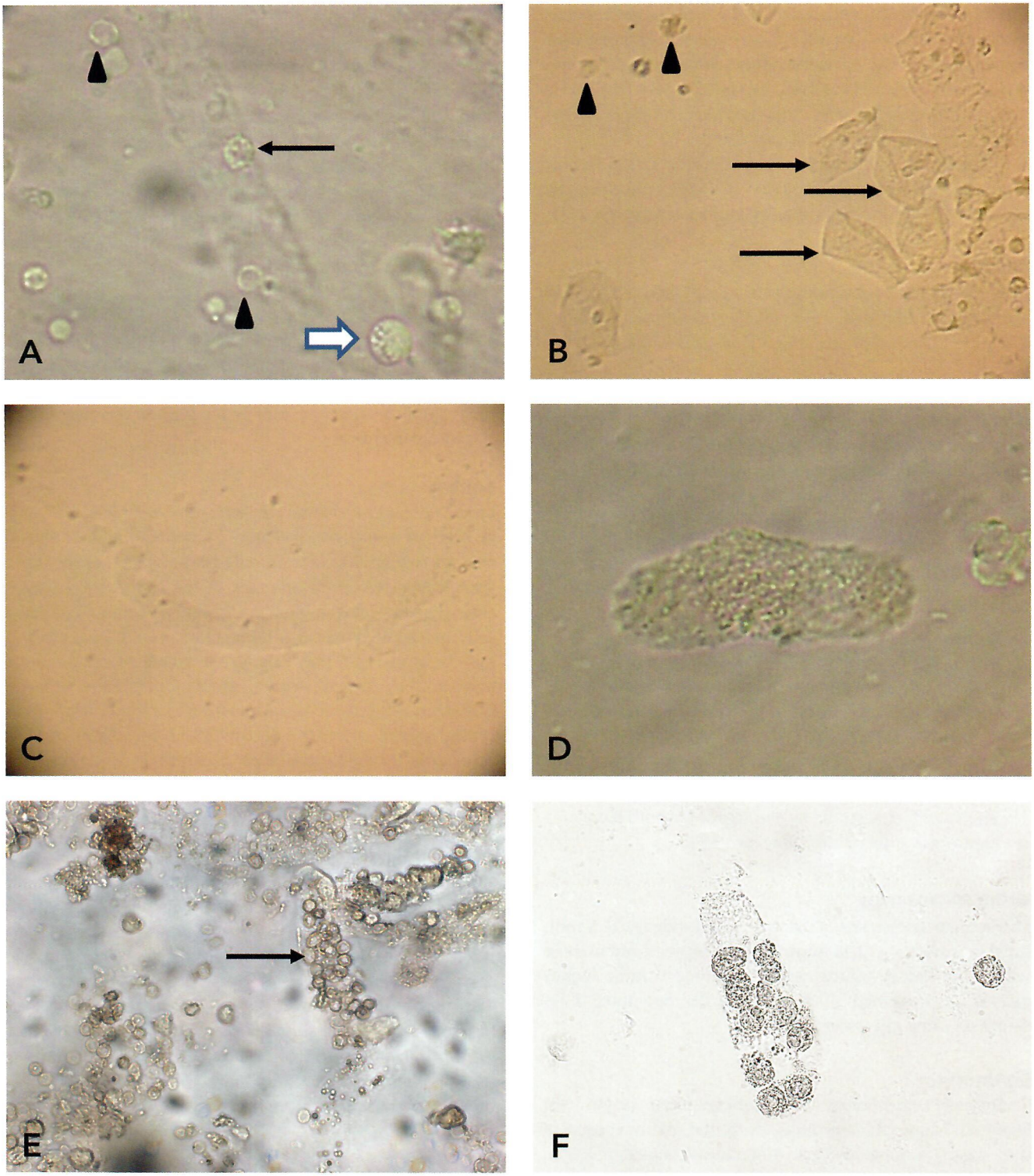


FIGURE 2. Findings on urine microscopy. **A,** Erythrocytes (*black arrowheads*) appear as small anucleated cells. Also shown is a leukocyte (*black arrow*) embedded in a cast, as well as a tubular cell (*white arrow*). **B,** Leukocytes (*black arrowheads*) are larger than erythrocytes and have characteristic granular cytoplasm: Note the large relative size of squamous epithelial cells (*black arrows*). **C,** Hyaline casts have a transparent, empty appearance. **D,** Granular casts may be coarse or fine in nature. Deeply pigmented (muddy brown) granular casts may be associated with acute tubular necrosis. **E,** Erythrocyte cast (*black arrow*). **F,** Leukocyte cast.

FIGURE 3. Urine microscopy demonstrating acanthocytes, indicated in the red circles. Acanthocytes, a form of dysmorphic erythrocytes characterized by vesicle-shaped protrusions, are most suggestive of glomerular bleeding.

Courtesy of J. Charles Jennette, MD.

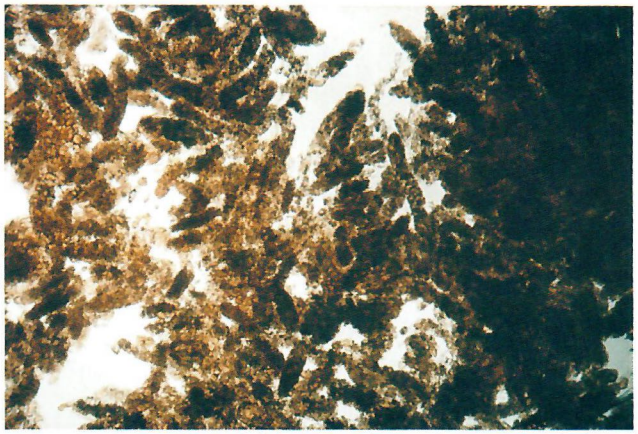
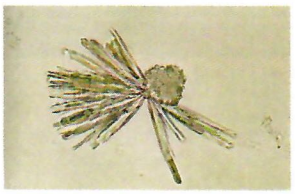
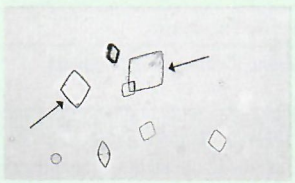
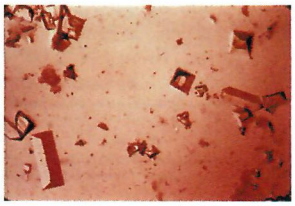
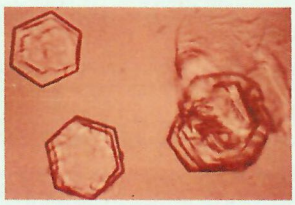


FIGURE 4. Tubular injury (for example, acute tubular necrosis) may lead to deposition of pigmented epithelial tubular debris in the proteinaceous matrix of the cast, with the formation of pigmented or granular (muddy brown) casts.

TABLE 3. Urine Crystals

Type	Morphology	Associated Conditions	Image
Calcium oxalate	Envelope; dumbbell; needle	Hypercalciuria; hyperoxaluria; calcium oxalate stones; ethylene glycol poisoning	
Calcium phosphate	Prism; needle; star-like clumps	Distal renal tubular acidosis; urine pH >6.5; tumor lysis syndrome; acute phosphate nephropathy	
Uric acid	Rhomboid; needle; rosette, barrels; hexagonal plates	Hyperuricemia; gout; diabetes mellitus; obesity; tumor lysis syndrome; urine pH <6.0	
Struvite (magnesium ammonium phosphate)	Coffin-lid	Alkaline urine due to chronic urinary tract infection with urease-producing organisms	
Cystine	Hexagonal	Cystinuria	

KEY POINTS

- Isomorphic erythrocytes suggest a nonglomerular origin of blood; dysmorphic erythrocytes, particularly acanthocytes, suggest a glomerular origin.
- Erythrocyte casts are highly suggestive of glomerulonephritis, leukocyte casts may be present in acute interstitial nephritis and infections, and granular (muddy brown) casts may be present in acute tubular necrosis.

Measurement of Albumin and Protein Excretion

Assessment for urine protein is indicated in patients with any suspected kidney disease. Concurrent increased serum creatinine or abnormal findings on urine sediment raise concern for active kidney disease in any patient with proteinuria.

Assays to detect protein in the urine include urine dipstick, random (spot) urine protein-creatinine ratio or albumin-creatinine ratio, and 24-hour urine collections. Because of the challenges of 24-hour urine collections, the random urine albumin-creatinine ratio and protein-creatinine ratio have been widely adopted. Both random tests detect albuminuria, but the urine protein-creatinine ratio also detects nonalbumin proteins. Random collections correlate well with timed collections and are sufficiently accurate for screening and monitoring proteinuria despite inaccuracies due to diurnal fluctuations of urine protein and interindividual differences in urine creatinine excretion. **Table 4** outlines the definitions of proteinuria and albuminuria as well as normal values.

Urine albumin, when present at high levels, indicates glomerular injury; conversely, the absence of albuminuria essentially excludes most glomerular diseases. Smaller proteins are filtered at the level of the glomerulus but are reabsorbed by the proximal tubule; their presence in urine generally indicates tubulointerstitial disease. Light chains present at high levels, such as in monoclonal gammopathy, are detected on urine protein electrophoresis or free light chain assay.

Transient, nonpathologic, usually small elevations in urine protein can occur with acute illness or fever, rigorous exercise, and pregnancy. Orthostatic proteinuria is a benign proteinuria that increases when the patient is upright but decreases when the patient is recumbent. This condition is more common in adolescents but should be considered in those up to age 30 years. Split urine collection (daytime versus nighttime collection that includes first morning void) can evaluate this diagnosis.

Although screening for proteinuria may be considered for high-risk patients, such as those with diabetes mellitus or hypertension, screening for proteinuria or chronic kidney disease should not be done in asymptomatic adults without risk factors for chronic kidney disease, as there is no proven benefit.

In patients with diabetes, urine albumin screening is recommended because of its ability to detect early disease. The American Diabetes Association recommends yearly assessment in patients with type 2 diabetes, and assessment after 5 years of disease in patients with type 1 diabetes. Once patients are taking an ACE inhibitor or angiotensin receptor blocker, there is no

TABLE 4. Definitions of Proteinuria and Albuminuria

Total Urine Protein			
Urine Collection Method	**Normal**	**Clinical Proteinuria**	
24-Hour excretion	<150 mg/24 h	≥150 mg/24 h	
Spot urine protein-creatinine ratio[a]	<50 mg/g ≈ ≤150 mg/24 h	≥150 mg/g ≈ >150 mg/24 h	
Urine Albumin			
Urine Collection Method	**Normal[b]**	**Moderately Increased Albuminuria[b,c]**	**Severely Increased Albuminuria[b,c]**
24-Hour excretion	<30 mg/24 h	30-300 mg/24 h	>300 mg/24 h
Conventional spot urine dipstick[d]	Negative	Negative	Positive
Albumin-specific spot urine dipstick[e]	<3.0 mg/dL Negative	≥3.0 mg/dL Positive	Positive
Spot urine albumin-creatinine ratio[a]	<30 mg/g ≈ <30 mg/24 h	30-300 mg/g ≈ 30-300 mg/24 h	>300 mg/g ≈ >300 mg/24 h

[a]Because of the difficulty of obtaining a 24-hour urine collection, urine protein-creatinine ratio or urine albumin-creatinine ratio on random (spot) urine samples is used to estimate 24-hour excretion. Measurement of either urine protein or albumin concentration in a sample is divided by the creatinine concentration of the same sample to derive a unitless value. These ratios correlate well with the 24-hour excretion of protein or albumin. Although these calculations are technically dimensionless, they may be expressed by different laboratories with their units of calculation, such as mg/g (mg protein or albumin/g creatinine) or with units to reflect the proportional 24-hour excretion amount (mg or g protein or albumin/g creatinine).

[b]Chronic kidney disease classification categories A1, A2, and A3 correspond to normal (or mildly increased, moderately increased, and severely increased albuminuria, respectively).

[c]The terminology of "moderately increased albuminuria" and "severely increased albuminuria" has been adopted because of the finding that even relatively low levels of urine protein have been associated with significant cardiovascular risk and risk for progression of underlying kidney disease.

[d]Conventional urine dipsticks are more sensitive for detection of albumin than nonalbumin proteins; the detection limit is approximately 30 mg/dL, although they are not highly accurate for determining the degree of albuminuria if present.

[e]Urine dipsticks designed specifically to detect small amounts of albuminuria. Similar to conventional urine dipsticks, these dipsticks detect albumin above a concentration threshold but are sensitive to the presence of albumin at lower levels and can be used to indicate the presence of moderately increased albuminuria.

evidence that monitoring proteinuria is beneficial or that reduced proteinuria translates into improved outcomes.

Urine protein electrophoresis can characterize proteins, allowing for classification of the proteinuria as glomerular or tubular. It also detects monoclonal gammopathy, although it is less sensitive than light chain assay.

KEY POINTS

HVC
- The random (spot) urine protein-creatinine ratio and albumin-creatinine ratio correlate with 24-hour urine collections and are sufficiently accurate for screening and monitoring proteinuria.
- High urine albumin levels indicate glomerular injury; the absence of albuminuria excludes most glomerular diseases.

HVC
- There is no need to monitor urine protein excretion in patients who are taking an ACE inhibitor or angiotensin receptor blocker.

Clinical Evaluation of Hematuria

Hematuria is defined as the presence of >3 erythrocytes/hpf in the urine sediment and may be microscopic (detectable only on urine testing) or macroscopic (grossly visible). Hematuria is most often of nonglomerular origin. A glomerular origin is suggested by concurrent proteinuria, presence of dysmorphic erythrocytes, increased serum creatinine or decrease in eGFR, or systemic signs and symptoms. Evaluation of hematuria is outlined in **Figure 5**.

Urinalysis should not be used for urothelial cancer screening in asymptomatic adults. However, a single incidental finding of hematuria is sufficient to warrant further investigation. Evaluation should be pursued even in patients with bleeding diatheses or those taking antiplatelet or anticoagulation therapy. If menstruation, viral illness, vigorous exercise, or other benign cause is suspected, urinalysis should be repeated after the cause is resolved. If infection is confirmed, urinalysis should be repeated after treatment to document resolution of hematuria.

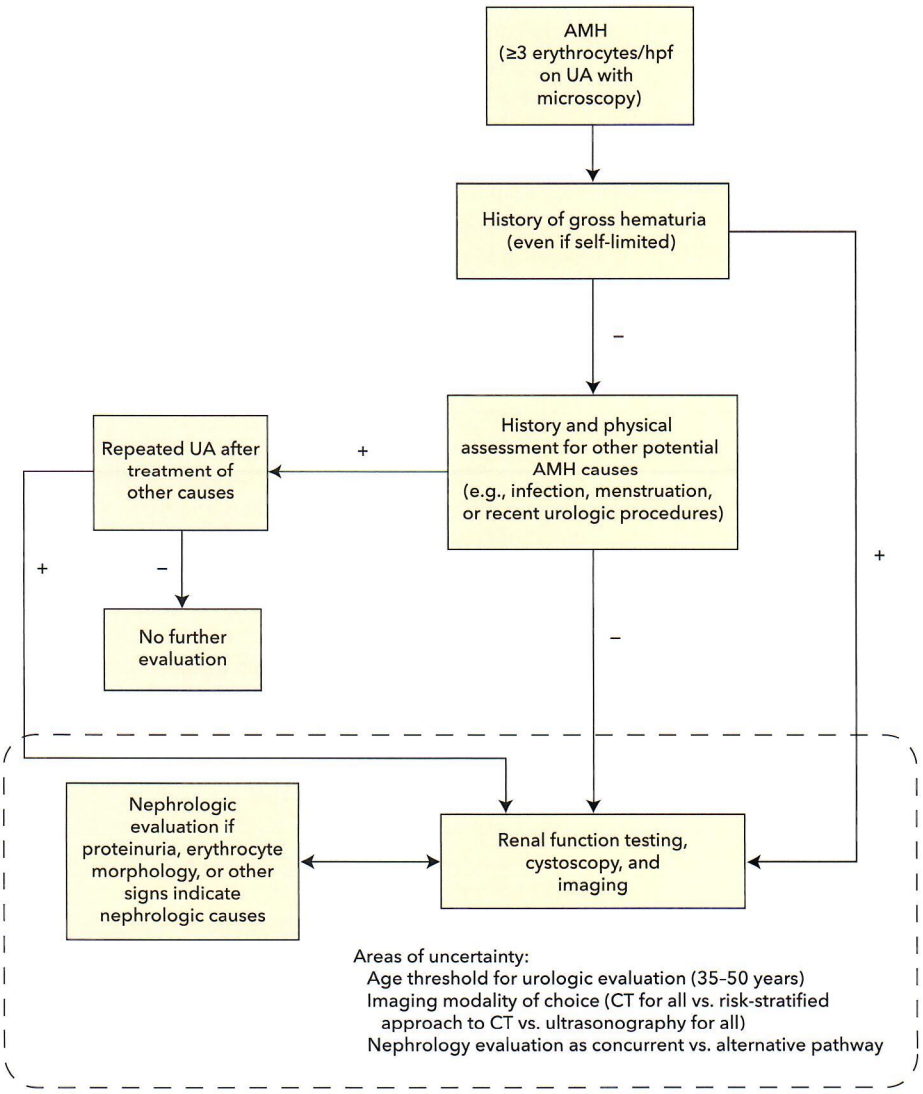


FIGURE 5. Summary of the American College of Physicians recommendations for the evaluation of patients with hematuria. AMH = asymptomatic microscopic hematuria; UA = urinalysis.

Reprinted with permission from Nielsen M, Qaseem A; High Value Care Task Force of the American College of Physicians. Hematuria as a marker of occult urinary tract cancer: advice for high-value care from the American College of Physicians. Ann Intern Med. 2016;164:488-97. [PMID: 26810935] doi:10.7326/M15-1496

TABLE 5. Additional Risk Factors for Urothelial Cancer
Irritative lower tract symptoms
Prior pelvic radiation therapy
Prior chemotherapy with cyclophosphamide or ifosphamide
Family history of urothelial cancer or Lynch syndrome
Occupational exposure to benzene, rubber, petrochemicals, and/or dyes
Chronic indwelling foreign body in the urothelial tract

In a patient with asymptomatic microhematuria, it is important to assess kidney function, erythrocyte morphology, and urine protein to evaluate for a nephrologic cause, particularly glomerulonephritis. The absence of proteinuria generally rules out a glomerular process; exceptions include very mild glomerular disease (most often IgA nephropathy) or thin glomerular basement membrane disease related to a type IV collagen defect that may present as isolated hematuria. Systemic signs and symptoms raise suspicion for nephrologic disease, particularly those associated with rheumatologic disorders and rapidly progressive glomerulonephritis.

Macroscopic hematuria should prompt urology referral even if self-limited, with further evaluation of nephrologic disease and malignancy as indicated.

If a nephrologic cause of hematuria is not suggested, hematuria may indicate a malignancy. The American Urological Association (AUA) guidelines recommend stratifying patients as having low, intermediate, or high risk for an underlying urothelial malignancy, with risk status dictating subsequent management. Low-risk patients are women <50 years of age and men <40 years of age who have never smoked, have 3 to 10 erythrocytes/hpf noted on a single urinalysis, and have no additional risk factors for urothelial cancer (**Table 5**). Low-risk patients should have a repeat urinalysis within 6 months and, if normal, require no additional evaluation. If repeat urinalysis continues to show hematuria, these patients are reclassified as intermediate risk (<25 erythrocytes/hpf) or high risk (>25 erythrocytes/hpf). Immediate kidney ultrasonography or ultrasonography plus cystoscopy is not inappropriate for low-risk patients and should be performed if the patient prefers a more aggressive approach. High-risk patients include those with any of the following features: >60 years of age, >30 pack-year history of smoking, >25 erythrocytes/hpf, or gross hematuria. High-risk patients require cystoscopy and CT urography, if there are no contraindications, or MR urography. Intermediate-risk patients include all others and require prompt kidney ultrasonography and cystoscopy. The American College of Physicians and the AUA recommend against obtaining urine cytology in the initial evaluation of hematuria.

KEY POINTS

HVC
- Urinalysis should not be used for urothelial cancer screening in asymptomatic adults.

(Continued)

KEY POINTS *(continued)*

- Evaluation of hematuria should be pursued even in patients with bleeding diatheses or those taking antiplatelet or anticoagulation therapy.
- Evaluation of nonglomerular hematuria is based on the patient's underlying risk for urothelial malignancy and ranges from repeat urinalysis in 6 months for low-risk patients to cystoscopy and CT urography for high-risk patients.
- If imaging is negative when evaluating patients with nonglomerular hematuria for renal malignancy, cystoscopy should be performed.

Imaging Studies

Ultrasonography is the most commonly used kidney imaging modality. It is easily available, safe, and relatively inexpensive. Ultrasonography can demonstrate hydronephrosis, kidney size and cortical thickness, echogenicity, and presence of cysts and tumors. Absence of hydronephrosis quickly rules out obstruction in most cases. Echogenicity is the ability of a tissue to "bounce back" or return the ultrasound signal and is recognized as brighter shades on the sonogram image. Echogenicity is nonspecific but implies acute or chronic parenchymal disease. Additionally, ultrasonography can measure pre- and postvoid bladder residual for evaluation of bladder dysfunction or outlet obstruction. Ultrasonography is also useful for uncomplicated nephrolithiasis; a positive ultrasound may be adequate for initial diagnosis. Ultrasonography is less useful in evaluating diseases (including stones) of the mid or distal ureter. Doppler ultrasonography may detect renal artery stenosis or renal vein thrombosis, but is highly user dependent.

CT is appropriate for patients with a nondiagnostic ultrasound or a more complicated presentation. Noncontrast helical CT is the gold standard for diagnosis of nephrolithiasis, and is appropriate for evaluating renal colic. Most stones can be detected, including small stones and those in the distal ureter not detected on ultrasound. It may provide information regarding stone composition and, because the entire urinary tract and abdomen are visualized, alternative diagnoses may be suggested.

CT urography (contrast-enhanced kidney-specific CT) is the test of choice for patients with unexplained hematuria and allows characterization of renal tumors and cysts. CT with contrast is valuable for imaging the renal vasculature. The use of intravenous contrast confers risk for contrast-associated nephropathy in patients with an eGFR <30 mL/min/1.73 m^2. Intra-arterial contrast confers higher risk, particularly with an eGFR <50 mL/min/1.73 m^2.

MRI with contrast is an alternative for evaluation of renal masses and cysts when CT cannot be performed. MR angiography for detection of renal artery stenosis, and venography for detection of renal vein thrombosis, can be performed with or without gadolinium-based contrast, although contrast provides optimal imaging. MR angiography and CT angiography

have mostly replaced standard angiography of renal arteries. Because of concerns for nephrogenic systemic fibrosis (NSF), group I gadolinium–based contrast agents are contraindicated in patients with an eGFR <30 mL/min/1.73 m^2. Group II gadolinium–based contrast agents are likely safe in this population, such that benefit generally outweighs the risk for NSF. See Chronic Kidney Disease for more information on NSF.

Radionuclide imaging provides the most accurate measurement of GFR (see Estimation of Glomerular Filtration Rate).

KEY POINTS

HVC

- Ultrasonography is the most commonly used imaging modality in the evaluation of the kidneys and upper urinary tract because of its safety, cost effectiveness, and availability.
- CT urography is the test of choice for patients with unexplained hematuria and allows characterization of renal tumors and cysts; noncontrast helical CT is the gold standard for diagnosis of nephrolithiasis, and CT with contrast is valuable in imaging the renal vasculature.

Kidney Biopsy

Clinical and laboratory features are often insufficient for definitive diagnosis of kidney disease. Kidney biopsy may therefore be essential for diagnosis and management. Indications include glomerular hematuria, severely increased albuminuria (formerly known as macroalbuminuria or overt proteinuria), acute or chronic kidney disease of unclear cause, and kidney transplant dysfunction or monitoring. AIN and atheroembolic disease may require biopsy for diagnosis because they frequently present only with increased serum creatinine.

Percutaneous kidney biopsy with ultrasonography or CT guidance is most common. Open or laparoscopic surgical biopsy is performed when percutaneous biopsy is not possible. Contraindications to percutaneous biopsy include the uncooperative patient, bleeding diatheses (including antiplatelet use or anticoagulation), uncontrolled hypertension, poor kidney visualization, atrophic kidneys, and active UTI. Solitary kidney and pregnancy require weighing of risks and benefits.

The most common and concerning risk of biopsy is retroperitoneal bleeding. Major bleeding complications, including the need for transfusion or angiography with or without embolization, and hemodynamic instability occur in <3% of biopsies. CT with contrast is the most effective noninvasive method to assess for large hematoma or an ongoing bleed. However, angiography provides definitive diagnosis of an ongoing bleed and allows for therapeutic intervention. Minor complications, including pain and hematuria, are more frequent. Kidney loss and death are very rare complications.

KEY POINT

- Indications for kidney biopsy include glomerular hematuria, severely increased albuminuria, kidney disease of unclear cause, and kidney transplant dysfunction or monitoring.

Fluids and Electrolytes

Osmolality and Tonicity

The osmolality of a solution is determined by the number of solutes per kilogram. In serum or plasma, osmolality can be measured or calculated using the following formula:

$$2 \times [Na^+] + \text{Glucose (mg/dL)}/18 + \text{Blood Urea Nitrogen (mg/dL)}/2.8 + \text{Ethanol (mg/dL)}/3.7 \text{ if present}$$

$$\text{If using international units: } 2 \times [Na^+] + \text{Urea (mmol/L)} + \text{Glucose (mmol/L)} + \text{Ethanol (mmol/L)} \times 1.25$$

Normal serum osmolality is between 275 and 295 mOsm/kg H_2O. The difference between measured osmolality and calculated osmolality (the osmolal gap) should be <10 mOsm/kg H_2O. A greater value suggests the presence of a low-molecular-weight alcohol. Because water moves freely between the intracellular and extracellular spaces based on the osmotic gradient, the osmolality of both compartments is virtually identical.

Osmolality is tightly controlled within a narrow range by thirst and antidiuretic hormone (ADH; also known as vasopressin). ADH stimulates reabsorption of water in the collecting duct of the kidney. Increases in tonicity stimulate both thirst and ADH. As long as there is access to water, appropriate thirst, normal control of ADH, and a functioning nephron, serum osmolality should be maintained in the normal range. Disorders of osmolality reflect impaired water homeostasis. Because the body will defend volume status over tonicity, volume depletion will stimulate ADH such that at any given osmolality, volume depletion will result in ADH release with risk for hyponatremia.

Disorders of Serum Sodium

Hyponatremia

Hyponatremia is defined as a serum sodium concentration <135 mEq/L (135 mmol/L). Evaluation begins with measurement of serum osmolality. Hyponatremia is then identified as hypertonic (osmolality >295 mOsm/kg H_2O), isotonic (osmolality 275–295 mOsm/kg H_2O), or hypotonic (osmolality <275 mOsm/kg H_2O) (**Figure 6**).

Evaluation

Symptoms caused by hyponatremia depend on both the rapidity and degree of decline in serum sodium. Acute hyponatremia in <48 hours provides inadequate time for the brain to adapt. A sudden drop in serum sodium causes water to move into brain cells, producing cerebral edema and possible headaches, seizures, or death. More chronic declines that allow cells to regulate their volume by decreasing intracellular electrolytes may be asymptomatic.

Hypertonic Hyponatremia

Hypertonic hyponatremia (osmolality >295 mOsm/kg H_2O) results from an increased concentration of effective osmotic

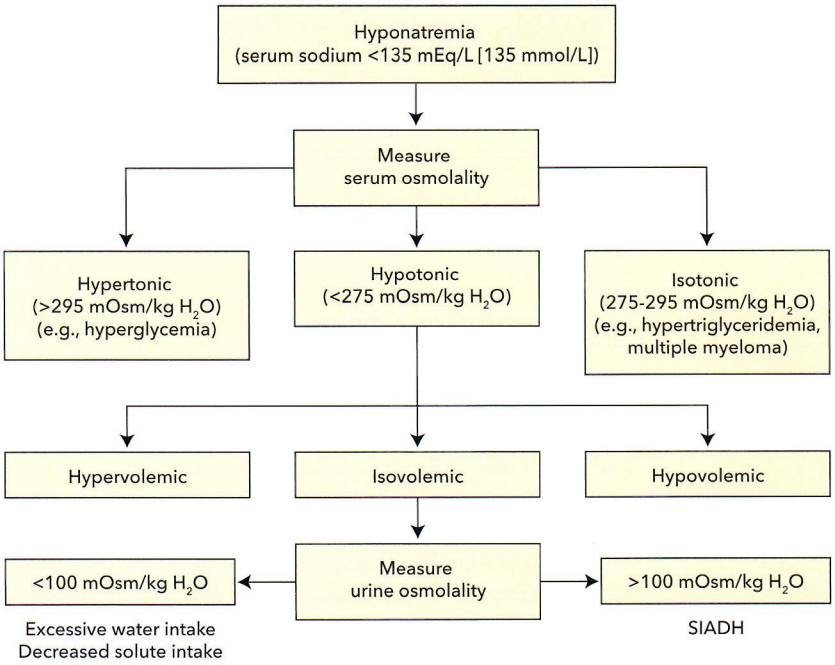


FIGURE 6. Evaluation of hyponatremia. SIADH = syndrome of inappropriate antidiuretic hormone secretion.

solute (typically glucose). The increase in osmolality pulls water out of cells, diluting the sodium. For every 100-mg/dL (5.6 mmol/L) increase in glucose, sodium decreases by 1.6 to 2.2 mEq/L (1.6-2.2 mmol/L).

Isotonic Hyponatremia

Isotonic hyponatremia (osmolality 275-295 mOsm/kg H_2O) is a laboratory artifact. Normally, plasma is 93% water (in which solutes are dissolved) and 7% solids (proteins and lipids). Conditions such as severe hypertriglyceridemia or multiple myeloma that increase the solid phase component of plasma will decrease the sodium concentration in plasma. Measurement of sodium using a direct ion-selective electrode will avoid this artifact.

Hypotonic Hyponatremia

Hypotonic hyponatremia (osmolality <275 mOsm/kg H_2O) reflects excess water for the sodium present and is further categorized by volume status into hypovolemic, hypervolemic, or isovolemic.

In hypovolemic hypotonic hyponatremia, volume depletion leads to renal sodium and water reabsorption stimulated by sympathetic outflow, angiotensin, aldosterone, and ADH, resulting in urine sodium concentration <20 mEq/L (20 mmol/L) and urine osmolality >300 mOsm/kg H_2O (except if taking diuretics or if secondary to renal salt wasting).

In hypervolemic hypotonic hyponatremia from heart failure or cirrhosis, effective circulating blood volume is inadequate despite total volume overload, resulting in urine chemistries similar to hypovolemic hyponatremia.

Isovolemic hypotonic hyponatremia is secondary either to impaired dilution of urine or to water intake that exceeds the kidney's ability to excrete dilute urine. Urine osmolality distinguishes between these two entities. Urine osmolality <100 mOsm/kg H_2O indicates excessive water intake, as seen with psychogenic polydipsia or poor solute intake. Because the kidney cannot excrete pure water, a minimal solute concentration of 50 mOsm/kg H_2O is required. If solute intake is low while liquid intake remains high (as seen in beer potomania or chronic low food intake), water excretion is limited by available urinary solute.

Isovolemic hypotonic hyponatremia with urine osmolality >100 mOsm/kg H_2O can occur in patients with late-stage chronic kidney disease because of impairment of urine dilution, causing hyponatremia after excessive dietary fluid intake. Urine osmolality >100 mOsm/kg H_2O also occurs in isovolemic hypotonic hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (**Table 6**). Medications are the most common cause of SIADH, with antidepressants and thiazide diuretics being the most common. 3,4-Methylenedioxymethamphetamine (ecstasy) can also cause hyponatremia. This drug stimulates ADH and, because of the associated fever and dry mouth, induces thirst. A frequent finding in SIADH is a low serum urate level (<4.0 mg/dL [0.24 mmol/L]). Cortisol and thyroid hormone are required to suppress ADH; therefore, deficiencies of these hormones should be evaluated.

Management

Treatment of hypotonic hyponatremia is determined by the underlying pathogenesis. In patients with volume overload, treatment is targeted to the underlying disease process along with water restriction. In hypovolemia, volume expansion with isotonic saline will suppress ADH, thereby increasing water excretion with correction of the hyponatremia.

Treatment of isovolemic hypotonic hyponatremia is determined by the severity of symptoms and the rapidity of the decline.

TABLE 6. Causes of the Syndrome of Inappropriate Antidiuretic Hormone Secretion

Cause	Examples
Drugs[a]	Thiazide diuretics
	Selective serotonin reuptake inhibitors
	Phenothiazines
	Haloperidol
	Clofibrate
	Carbamazepine
	Cyclophosphamide
	Tricyclic antidepressants
	Valproic acid
	3,4-Methylenedioxymethamphetamine (ecstasy)
Malignancy	Small cell lung carcinoma
	Squamous cell carcinoma of the head and neck
Central nervous system disease	Stroke, hemorrhage, infection, trauma, and psychosis
Pulmonary disease	Pneumonia (viral, bacterial, tuberculous)
Endocrine disorders	Glucocorticoid deficiency
	Myxedema
Idiopathic	Mostly in older patients; some cases later noted to be occult tumor (neuroblastoma, small cell carcinoma)
Endurance exercise (marathon running)	–

[a]Drugs are the most common cause.

Symptomatic patients with isovolemic hypotonic hyponatremia (serum sodium typically <120 mEq/L [120 mmol/L]) and an acute decrease in serum sodium should be treated with a 100-mL bolus of 3% saline to increase the serum sodium by 2.0 to 3.0 mEq/L (2.0-3.0 mmol/L). If symptoms persist, the bolus can be repeated once or twice at 10-minute intervals as long as the serum sodium can be measured. If the acute decline in sodium is secondary to excess water intake, fluid restriction will rapidly correct the hyponatremia.

In isovolemic hypotonic hyponatremia with a more chronic (>48 hours' presentation) decline in serum sodium, overly aggressive treatment can result in neuronal damage and osmotic demyelination. Accordingly, unless it is documented that the hyponatremia is acute, all cases should be treated as chronic. The osmotic demyelination syndrome is characterized by varied neurologic manifestations, including paresis, movement disorders, behavioral abnormalities, seizures, and obtundation, which are usually irreversible. Patients at greatest risk have severe hyponatremia (Na^+ <105 mEq/L [105 mmol/L]) that is chronic and often associated with liver disease, malnutrition, or hypokalemia. The goal of initial therapy is to increase the serum sodium by 4.0 to 6.0 mEq/L (4.0-6.0 mmol/L) in a 24-hour period, and not to exceed 8.0 mEq/L (8.0 mmol/L) in 24 hours. If there is significant neurologic impairment (e.g., seizures or coma), sodium can be acutely increased 2.0 to 4.0 mEq/L (2.0-4.0 mmol/L) using either a bolus or a continuous 30-mL/h infusion of 3% saline, with frequent monitoring of the urine volume and serum sodium. Simultaneous administration of desmopressin makes the rate of correction resulting from 3% saline more predictable and safer for the patient because it prevents an unexpected water diuresis and rapid increases in the serum sodium.

In patients with asymptomatic isovolemic hypotonic hyponatremia or with minimal symptoms (headache, lethargy), water restriction is safe and effective. However, limiting fluid intake to <800 mL/24 h is often intolerable. If water restriction is not adequate, therapy is targeted at blocking ADH activity or increasing water excretion. Demeclocycline inhibits ADH action and can be used chronically but is frequently associated with photosensitivity and gastrointestinal symptoms. Tolvaptan, an ADH antagonist, is effective and usually well tolerated, but it is cost-prohibitive and its use is limited to 1 month because of potential liver toxicity. Although loop diuretics can be used adjunctively to limit urine concentration, along with increased oral sodium intake, a recent randomized study showed no therapeutic benefit in patients treated with water restriction alone versus water restriction plus furosemide with or without salt supplementation. Patients treated with furosemide had a higher likelihood of acute kidney injury and hypokalemia. Oral urea, 15 to 30 g/d, is also effective in increasing water excretion, although its use is often limited because of unpalatable taste.

KEY POINTS

- Treatment of symptomatic isovolemic hypotonic hyponatremia consists of a 100-mL bolus of 3% saline.
- The therapeutic goal for acute isovolemic hypotonic hyponatremia is an increase in serum sodium by 2.0 to 3.0 mEq/L (2.0-3.0 mmol/L) and 4.0 to 6.0 mEq/L (4.0-6.0 mmol/L) for chronic isovolemic hypotonic hyponatremia.
- Overly aggressive treatment of chronic isovolemic hypotonic hyponatremia can result in osmotic demyelination.

Hypernatremia

Hypernatremia is defined as a serum sodium concentration >145 mEq/L (145 mmol/L). Although less common than hyponatremia, hypernatremia is often seen in hospitalized patients and is associated with increased mortality in the critically ill.

Hypernatremia can be divided into three broad categories: inappropriate intake/administration of hypertonic solutions; loss of hypotonic fluids; and excessive water loss due to defects in ADH release or action. A detailed history and physical examination combined with measurement of urine electrolytes and osmolality help distinguish the pathogenesis of hypernatremia.

Evaluation

The most common cause of hypernatremia is loss of hypotonic body fluids with inadequate water replacement due to lack of access or absence of thirst. Hypotonic losses may result from diarrhea, the respiratory tract, excessive sweating, or renal losses from osmotic diuresis (such as with glucosuria). If the losses are nonrenal, urine osmolality will be elevated to >600 mOsm/kg H_2O. In osmotic diuresis, urine osmolality is usually between 300 and 600 mOsm/kg H_2O. Hypotonic losses with inadequate replacement result in intravascular volume depletion with orthostasis or frank hypotension.

Hypertonic hypernatremia can also occur with administration of excessive quantities of hypertonic saline or sodium bicarbonate, or with salt ingestion. The acute increase in sodium causes water to move out of brain cells, causing shrinkage and neurologic findings. Symptoms can range from lethargy to seizures and coma. Physical examination frequently reveals intravascular volume overload.

Less commonly, hypernatremia may be secondary to either an inadequate release (central diabetes insipidus) or action of ADH (nephrogenic diabetes insipidus). Central diabetes insipidus can result from tumors that invade the hypothalamus, infiltrating diseases such as sarcoidosis, or surgical destruction. Nephrogenic diabetes insipidus is often caused by drugs such as lithium. Common symptoms are polydipsia and polyuria. Urine osmolality <300 mOsm/kg H_2O in a hypernatremic patient confirms the diagnosis. An increase in urine osmolality after a dose of desmopressin (ADH analogue) distinguishes between central and nephrogenic diabetes insipidus. Because solute loss is not excessive, hypernatremia from water loss is usually associated with minimal symptoms unless the sodium increases acutely.

Management

Management of hypernatremia is determined by the underlying pathogenesis. When secondary to acute hypertonic gains, treatment needs to rapidly restore normal sodium concentration. Water can be administered as 5% dextrose. The goal is to replace the entire water deficit within 24 hours.

If hypernatremia has occurred over >24 hours, the brain adapts by uptake of electrolytes and other osmotically active solutes. Although rapid correction of sodium could theoretically cause cerebral edema, this does not seem to occur in adults, and decreases as much as 1 mEq/h (1 mmol/h) appear to be well tolerated. Nevertheless, most authorities would correct at a rate ≤0.5 mEq/h (0.5 mmol/h), with a goal correction of 10 to 12 mEq/L/d (10-12 mmol/L/d). Water deficit or volume of replacement water required is estimated using the formula:

$$(\text{Total Body Water}) \times [(\text{Current Sodium} - \text{Ideal Sodium})/\text{Ideal Sodium}]$$

The change in the serum sodium for each liter of infusate can be calculated using the formula:

$$(\text{Infusate Sodium}) - (\text{Serum Sodium}) \div (\text{Total Body Water} + 1)$$

Total body water is usually estimated as 60% and 50% of lean body weight in young men and women, respectively, and approximately 50% and 45% in older men and women, respectively.

If possible, water should be administered orally or by means of a nasogastric tube. Because dextrose-containing solutions may cause glycosuria and increased free water losses, it is important to monitor serum glucose and maintain it below 180 mg/dL (10 mmol/L). In the presence of hemodynamic compromise due to intravascular volume depletion, replacement fluid should be isotonic saline; otherwise, a hypotonic solution (half [0.45%] normal saline) can be used.

In patients with diabetes insipidus, the first step is determining whether the defect is secondary to a defect in ADH secretion or an ADH action. Central diabetes insipidus can be treated with intranasal or oral desmopressin, a synthetic analogue of vasopressin. Nephrogenic diabetes insipidus is more difficult to treat. Therapy is aimed at limited solute intake to decrease the amount of free water that the kidney can excrete and induction of mild volume depletion using a thiazide diuretic to increase salt and water reabsorption proximal to the collecting duct. The polyuria associated with lithium-induced nephrogenic diabetes insipidus can be ameliorated with the addition of amiloride, which reduces lithium uptake by the principal cell of the cortical collecting tubule.

KEY POINTS

- The most common cause of hypernatremia is loss of hypotonic body fluids with inadequate water replacement due to lack of access or thirst.
- If hypernatremia has occurred over >24 hours, correction should be ≤0.5 mEq/h (0.5 mmol/h) to prevent cerebral edema.
- In the presence of hypernatremia due to intravascular volume depletion, replacement fluid should be isotonic saline; otherwise, a hypotonic solution (half [0.45%] normal saline) can be used.

Disorders of Serum Potassium

Hypokalemia

Hypokalemia is defined as a serum potassium level <3.5 mEq/L (3.5 mmol/L). It can be divided into disorders of internal balance (movement of potassium between the intracellular and extracellular compartments) and disorders of external balance (potassium intake and output) (**Figure 7**). Serum potassium >3.0 mEq/L (3.0 mmol/L) is usually asymptomatic. Because the ratio of intracellular to extracellular potassium is the major determinant of the membrane potential of electrically active tissue, symptoms of hypokalemia include weakness or paralysis, decreased gastrointestinal motility or ileus, and cardiac arrhythmias. ECG manifestations include ST-segment depression, decreased T-wave amplitude, and increased U-wave amplitude (**Figure 8**). Severe hypokalemia can cause rhabdomyolysis.

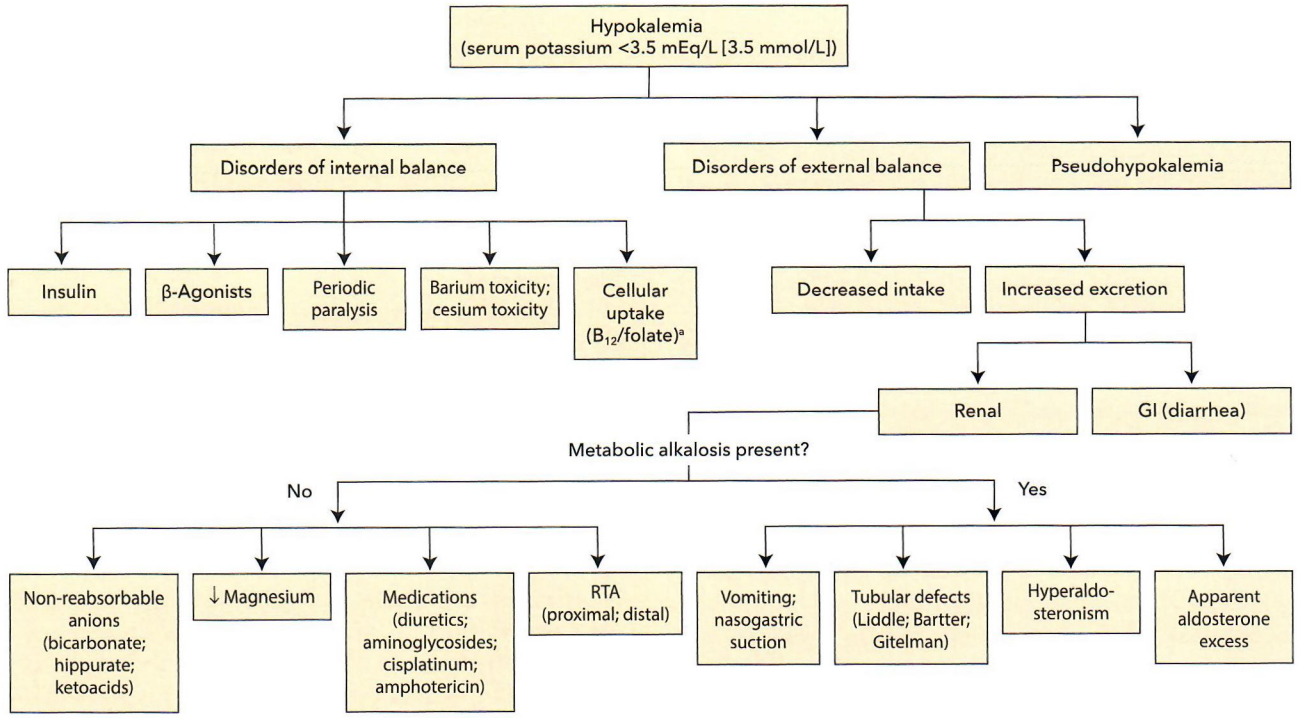


FIGURE 7. Causes of hypokalemia. GI = gastrointestinal; RTA = renal tubular acidosis.

[a]Treatment of megaloblastic anemia (B_{12}/folate deficiency).

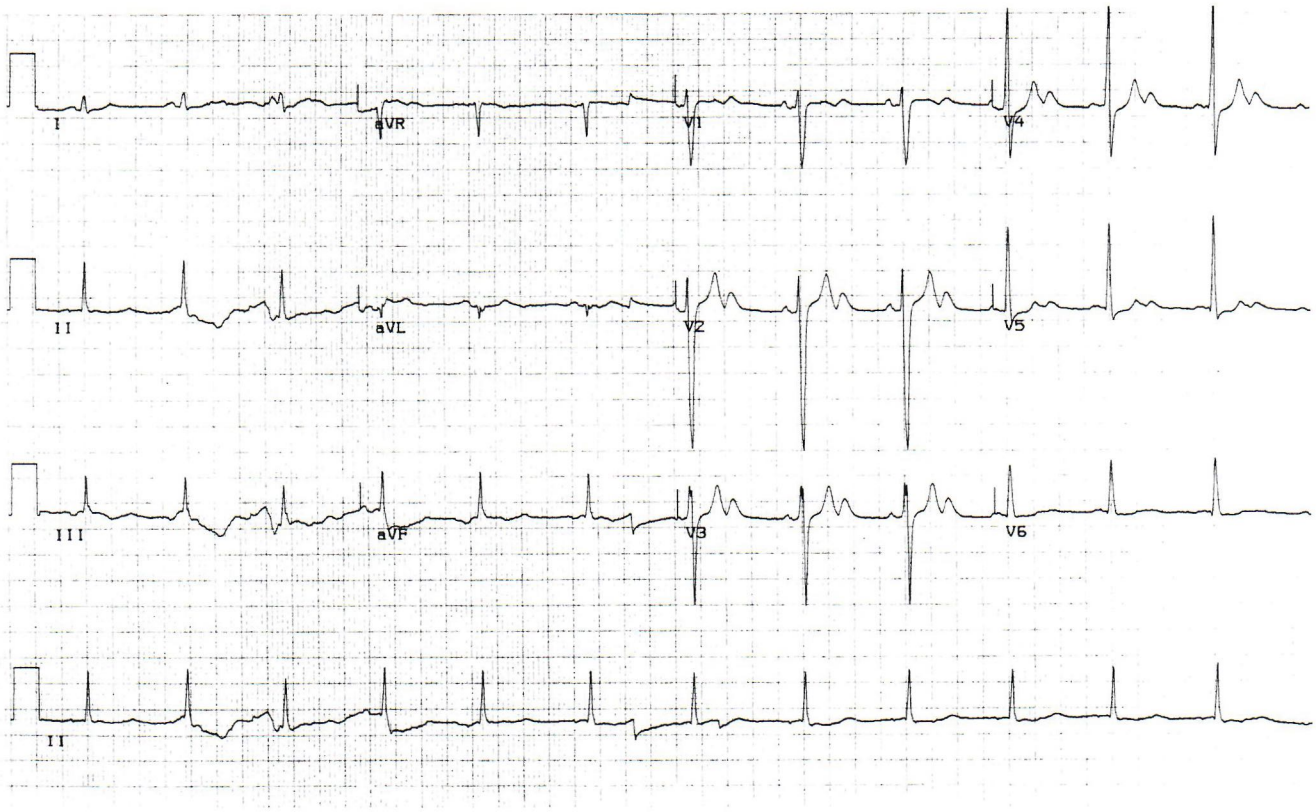


FIGURE 8. Hypokalemia is responsible for the changes on the ECG. The characteristic ECG finding in hypokalemia is the appearance of a U wave after the T wave, eventually replacing the T wave. Initially, T waves decrease in amplitude, and the ST segment flattens. Then U waves appear after the T waves, as seen in this image. The U waves ultimately replace the T waves completely; this may give the impression of QT prolongation, but it is a QU interval.

Evaluation

The cause of hypokalemia can usually be determined from the history and simple laboratory evaluation. Rarely, hypokalemia is spurious, as can occur in leukemia when delayed sample processing allows large numbers of metabolically active leukocytes to take up potassium. In addition to leukocytosis, a clue to pseudohypokalemia is the lack of signs and symptoms associated with hypokalemia.

Hypokalemia can occur secondary to disordered internal balance. Insulin or β_2-agonists shift potassium into cells, causing an acute, transient, and modest hypokalemia that is usually asymptomatic. Ingestion of soluble barium or cesium salts, which block potassium exit from cells, can produce severely symptomatic hypokalemia with levels below 2.0 mEq/L (2.0 mmol/L). Increased cell production after repletion of vitamin B_{12} or folate in deficient individuals can also cause hypokalemia. Hypokalemic periodic paralysis, either an inherited autosomal dominant disorder or an acquired disorder seen in patients with hyperthyroidism usually of Japanese descent, may present with severe muscle weakness and paralysis.

Most cases of hypokalemia are due to disordered external balance with total body potassium depletion, usually from increased potassium excretion. Because the kidney can almost cease potassium excretion, only a severely compromised diet can cause hypokalemia. The major determinants of renal potassium secretion are distal tubular flow rate and aldosterone, both of which increase sodium reabsorption, increasing the electronegativity of the tubule lumen and promoting potassium secretion. Under normal conditions, distal flow and aldosterone levels are inversely related, thus preventing disruptions in potassium homeostasis by changes in intravascular volume.

The gold standard to distinguish between renal and extrarenal causes of total body potassium depletion is a 24-hour urine potassium <30 mEq/24 h (30 mmol/d); however, this test is often impractical. The preferred alternative is a spot urine potassium-creatinine ratio. A value <13 mEq/g identifies hypokalemia secondary to lack of intake, transcellular shifts, or gastrointestinal losses.

Gastrointestinal losses are usually caused by diarrhea or laxative abuse. Frequently, a concomitant metabolic acidosis is present. Renal potassium wasting may be caused by numerous disorders, including medications (most commonly diuretics), delivery of non-reabsorbable anions (such as bicarbonate) to the distal tubule, aldosterone excess, hypomagnesemia, and tubular defects (see Figure 8).

Hyperaldosteronism is associated with hypertension and a metabolic alkalosis. Hypomagnesemia can cause potassium wasting, and renal potassium wasting also occurs in inherited tubular defects, including Liddle, Bartter, and Gitelman syndromes. In Liddle syndrome, increased sodium reabsorption in the distal nephron causes hypertension, metabolic alkalosis, and potassium wasting. Bartter and Gitelman syndromes are caused by mutations in transporters that mimic the effects of diuretics on the tubule (e.g., mimicking loop diuretics in Bartter syndrome and thiazides in Gitelman syndrome). In Bartter syndrome, urinary calcium excretion is normal or increased, whereas in Gitelman syndrome, hypocalciuria occurs. Finally, proximal and distal renal tubular acidosis is associated with potassium wasting.

Management

The total body potassium deficit is difficult to predict and can be up to 200 mEq (200 mmol) for each mEq/L (mmol/L) decrease in plasma potassium. In patients with neuromuscular or cardiac symptoms, it is important to increase the potassium promptly. Intravenous potassium can be safely infused at 20 mEq/h (20 mmol/h). Infusion through a central vein can be increased to 40 mEq/h (40 mmol/h) with close monitoring. For mild hypokalemia (2.5–3.5 mEq/L [2.5–3.5 mmol/L]), oral supplementation using potassium chloride or potassium bicarbonate is usually adequate. Concurrent hypomagnesemia must be corrected to prevent ongoing potassium losses. In patients with potassium wasting, potassium-sparing diuretics can be helpful. When significant hypokalemia is secondary to acute transcellular shifts, total body potassium is normal and excessive potassium replacement may cause rebound hyperkalemia.

KEY POINTS

- ECG manifestations of hypokalemia include ST-segment depression, decreased T-wave amplitude, and increased U-wave amplitude.
- In patients with hypokalemia and neuromuscular or cardiac symptoms, intravenous potassium (20 mEq/h [20 mmol/h]) can be used to increase the potassium promptly.

Hyperkalemia

Hyperkalemia is defined by a serum potassium level >5.0 mEq/L (5.0 mmol/L). Levels >6.0 mEq/L (6.0 mmol/L) can cause fatal arrhythmias. Slow increases in potassium are better tolerated than abrupt increases. Signs and symptoms of hyperkalemia are manifested in electrically active tissue and include muscle weakness and ECG abnormalities.

Evaluation

Initial evaluation of hyperkalemia requires a history and physical examination, review of all medications, assessment of kidney function, and an ECG. Initial ECG manifestations include peaked precordial T waves and a shortened QT interval. With progression of hyperkalemia, lengthening of the PR interval, loss of the P wave, widening of the QRS complex, a sine wave pattern, and asystole may occur (**Figure 9**). However, ECG findings do not always correlate with the serum potassium level and do not necessarily progress in an orderly fashion.

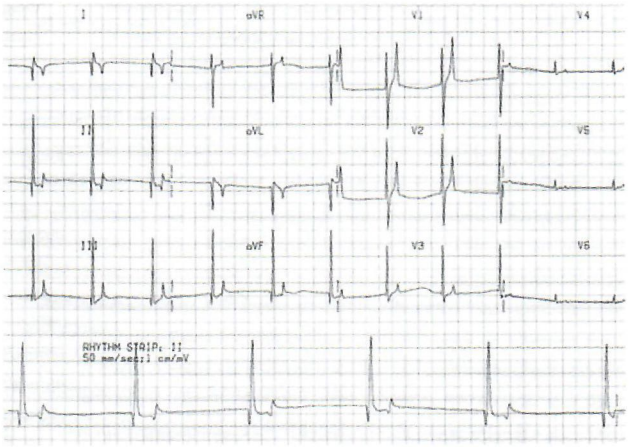


FIGURE 9. This ECG demonstrates tall, peaked T waves and decreased P waves, which are characteristic of hyperkalemia. In experimental models of increasing potassium, there are progressive changes in the ECG beginning with peaked T waves, PR prolongation, loss of P waves, widening of QRS, and finally sinusoidal waveform. This, however, is not necessarily true in clinical situations.

During the clotting process, cells are disrupted with the release of intracellular potassium, and pseudohyperkalemia may occur in serum specimens when there are extreme elevations of leukocytes or platelets. In these cases, a repeat plasma specimen will be normal. A tight tourniquet or excessively clenched fist during blood draw can also cause local potassium release.

Hyperkalemia may be caused by transcellular shifts, as occur in states of insulin deficiency or hypertonicity, or with the use of β_2-adrenergic blockers. Rapid breakdown of cells such as that seen in rhabdomyolysis or tumor lysis syndrome can acutely raise serum potassium levels.

Hyperkalemia usually results from increased intake with decreased renal excretion. Hyperkalemia frequently occurs with oliguric acute or chronic kidney disease with a glomerular filtration rate (GFR) <20 mL/min/1.73 m^2. Potassium-sparing diuretics (amiloride, triamterene, spironolactone) also commonly cause hyperkalemia through decreased excretion. Other medications that decrease potassium excretion include trimethoprim and pentamidine (by blocking the epithelial sodium channel) and NSAIDs (by decreasing renin). Hypoaldosteronism caused by ACE inhibitors, angiotensin receptor blockers, heparin, type 4 renal tubular acidosis (often seen in diabetic kidney disease), or primary adrenal insufficiency also causes hyperkalemia, especially in the presence of excess potassium intake or volume depletion.

Management

Elevation in the serum potassium level >6.5 mEq/L (6.5 mmol/L), or >6.0 mEq/L (6.0 mmol/L) with ECG changes, should be promptly treated. Treatment is directed at stabilizing the cardiac membrane, shifting potassium into cells, and removing potassium from the body. Intravenous administration of calcium gluconate quickly antagonizes the effects of hyperkalemia on the cardiac membrane. Its duration of action is relatively short and therefore is never definitive therapy. Intravenous administration of insulin alone if serum glucose is >250 mg/dL (13.9 mmol/L) or with 10% dextrose will drive potassium into cells, and is effective for up to 6 hours. Potassium can also be shifted into cells using high-dose nebulized albuterol. Sodium bicarbonate therapy has fallen out of favor because it does not promote redistribution of potassium.

Definitive treatment of severe hyperkalemia, unrelated to reversible transcellular shift, must include removal of potassium from the body. In patients without severe kidney disease, loop diuretics can be effective. Use of the potassium exchange resin sodium polystyrene sulfonate is controversial; its effectiveness is limited, and it produces adverse gastrointestinal effects, including volume overload and, rarely, bowel necrosis. Patiromer and sodium zirconium cyclosilicate bind potassium in the gastrointestinal tract and effectively lower potassium. Hemodialysis is the treatment of choice in patients with severe hyperkalemia and oliguric kidney disease.

Chronic hyperkalemia is often overtreated and, in the absence of signs of cardiac toxicity, does not warrant the emergent interventions. Limiting potassium intake may be beneficial, and increased sodium intake along with a thiazide or loop diuretic will increase potassium excretion. In hypoaldosteronism, fludrocortisone will normalize the potassium; however, it may cause elevated blood pressure and edema, and long-term effects of fludrocortisone are unknown. All potentially causative medications should be discontinued if possible. If necessary, potassium binders may allow continuation of essential medications.

KEY POINTS

- Intravenous administration of calcium gluconate quickly antagonizes the effects of hyperkalemia on the cardiac membrane.
- Definitive treatment of severe hyperkalemia must include removal of potassium from the body; patiromer and sodium zirconium cyclosilicate can increase gastrointestinal excretion, loop diuretics can be effective in patients without severe kidney disease, and hemodialysis is the treatment of choice in patients with severe hyperkalemia and oliguric kidney disease.

Disorders of Serum Phosphate

Hypophosphatemia

Hypophosphatemia is defined as a serum phosphate level <2.7 mg/dL (0.87 mmol/L). Phosphate (PO_4) is found primarily within bone and the intracellular space. Phosphate is required for metabolic pathways involved in energy production, cellular repair, and enzymatic activity. Levels <2.0 mg/dL (0.65 mmol/L) are associated with muscle weakness. Severe hypophosphatemia (<1.0 mg/dL [0.32 mmol/L]) is associated with life-threatening symptoms, including delirium, seizures, coma, heart failure, respiratory failure, rhabdomyolysis, and hemolysis.

Evaluation

Hypophosphatemia results from transcellular shifts, decreased intake, or increased excretion. Movement of phosphorous into cells occurs with respiratory alkalosis, insulin treatment, refeeding of starved individuals, or, less commonly, as part of the hungry bone syndrome following parathyroidectomy or with prolonged exposure to continuous renal replacement therapy. Ferric carboxymaltose, an intravenous iron preparation, has been associated with hypophosphatemia by causing renal phosphate wasting. Medications that bind phosphate in the gut (calcium, antacids) can decrease effective intake. Because the kidney can decrease phosphate excretion to very low levels, low dietary phosphate rarely causes hypophosphatemia without coexisting malnutrition. Increased excretion may be caused by diarrhea or renal wasting. Excretion of >100 mg of phosphate in a 24-hour urine collection or a fractional excretion of phosphate ($FEPO_4$) >5% suggests renal wasting. Renal losses of phosphate are seen in hyperparathyroidism and in proximal tubular dysfunction.

Management

Mild decreases in serum phosphate can be treated with oral sodium or potassium phosphate. Levels <2.0 mg/dL (0.65 mmol/L) should be treated with intravenous sodium phosphate. Calcitriol is sometimes required to increase intestinal absorption of phosphate.

KEY POINTS

- Severe hypophosphatemia (<1.0 mg/dL [0.32 mmol/L]) is associated with life-threatening symptoms, including delirium, seizures, coma, heart failure, respiratory failure, rhabdomyolysis, and hemolysis.
- Mild hypophosphatemia can be treated with oral sodium or potassium phosphate; levels <2.0 mg/dL (0.65 mmol/L) should be treated with intravenous sodium phosphate.

Hyperphosphatemia

Hyperphosphatemia is defined by a serum phosphate level >4.5 mg/dL (1.45 mmol/L). Symptoms are usually related to co-occurring hypocalcemia. Acute elevations in phosphate can cause precipitation of calcium phosphate in the kidney, resulting in phosphate nephropathy.

Evaluation

Hyperphosphatemia from reduced renal excretion does not occur due to reduced GFR unless patients have severe chronic kidney disease. Hypoparathyroidism decreases excretion through increased phosphate tubular reabsorption; hypocalcemia is often present. Rare defects in the action of fibroblast growth factor 23 (such as in tumoral calcinosis) also increase tubular reabsorption of phosphate.

Because phosphate is primarily an intracellular anion, widespread cellular damage as occurs in rhabdomyolysis and tumor lysis syndrome increases serum phosphate, especially if the GFR is decreased. Hyperphosphatemia can also be associated with diabetic ketoacidosis and, less commonly, lactic acidosis. Excessive phosphate intake rarely causes hyperphosphatemia because the kidney rapidly excretes phosphate. However, phosphate-containing cathartics can cause acute elevations in serum phosphate, especially in patients with reduced GFR.

Management

If kidney function is adequate, serum phosphate levels should normalize in 12 to 24 hours. If necessary, phosphate excretion can be increased with intravenous saline. In patients with impaired kidney function, dialysis may be necessary. Because many foods contain phosphate, dietary phosphate restriction is difficult. Therefore, patients with chronic hyperphosphatemia must often use agents that bind phosphate in the gastrointestinal tract to prevent absorption. See Chronic Kidney Disease for more information.

KEY POINTS

- Causes of hyperphosphatemia include cellular lysis with release of phosphate, excessive intake, and/or decreased renal excretion from decreased glomerular filtration rate or increased tubular reabsorption (hypoparathyroidism).
- If kidney function is adequate in patients with hyperphosphatemia, serum phosphate levels should normalize in 12 to 24 hours; if necessary, phosphate excretion can be increased with intravenous saline, and dialysis can be initiated for those with impaired kidney function.

Disorders of Serum Magnesium

There are approximately 24 grams of magnesium in the body, with 99% residing intracellularly and within bone. Magnesium is essential for protein and nucleic acid synthesis, cell adhesion, enzyme reactions, and modulating channel activity.

Hypomagnesemia

Hypomagnesemia is defined by a serum magnesium level <1.7 mg/dL (0.7 mmol/L). Symptoms usually do not develop until serum magnesium is <1.2 mg/dL (0.5 mmol/L). Symptoms include tremors, fasciculations, muscle weakness, carpopedal spasm, Chvostek (contraction of the ipsilateral facial muscles by tapping the facial nerve) and Trousseau (carpopedal spasm after inflation of blood pressure cuff above systolic blood pressure) signs, and seizures. Hypomagnesemia also appears to potentiate cardiac arrhythmogenicity due to hypokalemia, myocardial ischemia, and various drugs. In addition, hypomagnesemia causes hypokalemia due to renal potassium wasting, and it causes hypocalcemia by impeding parathyroid hormone release and action.

Evaluation

Hypomagnesemia results from decreased gastrointestinal absorption or increased renal secretion. History and physical examination often delineate the cause. More than 10 mg of

magnesium in a 24-hour urine collection or a fractional excretion of magnesium (FE_{Mg}) >2% suggests renal wasting in the setting of hypomagnesemia.

Causes of decreased magnesium absorption include severe malnutrition, diarrhea, and malabsorption. Proton pump inhibitors is an important cause of hypomagnesemia, with most reported cases occurring after prolonged use, which rapidly reverses upon discontinuation of the drug.

Hypomagnesemia from renal losses occurs with diuretics, cisplatin, aminoglycosides, or calcineurin inhibitors. Vascular endothelial growth factor inhibitors used in cancer treatment can cause significant magnesium wasting. Other causes of urine losses include volume expansion, alcohol ingestion, and diabetic ketoacidosis.

Management

If significant symptoms are present, 4 grams of magnesium sulfate should be infused over 12 hours and repeated if necessary. Importantly, half of acutely infused intravenous magnesium is excreted by the kidney; therefore, slow-release oral magnesium or nasogastric tube delivery may be better to replete mild to moderate hypomagnesemia.

KEY POINTS

- Significant symptoms of hypomagnesemia usually develop when the serum magnesium level is <1.2 mg/dL (0.5 mmol/L); these include tremors, fasciculations, muscle weakness, carpopedal spasm, Chvostek and Trousseau signs, seizures, and cardiac arrhythmias.
- Treatment of significant symptoms of hypomagnesemia includes magnesium sulfate infusions; less severe symptoms can be treated with slow-release oral magnesium.

Hypermagnesemia

Hypermagnesemia is defined by a serum magnesium level of >2.4 mg/dL (0.99 mmol/L).

Evaluation

Hypermagnesemia occurs infrequently and most commonly results from excessive intake in the setting of decreased kidney function. Antacids and laxatives contain magnesium, and therapeutic infusions of magnesium sulfate for refractory asthma and prevention of eclampsia are potential causes of hypermagnesemia.

Symptoms of hypermagnesemia do not occur until levels are 4.8 mg/dL (1.98 mmol/L). Early symptoms include loss of deep tendon reflexes, progressing to flaccid paralysis at higher levels. Hypermagnesemia also results in hypotension from loss of vascular tone. Laboratory analysis often shows hypocalcemia.

Management

Prevention is the key to management of hypermagnesemia. Hypermagnesemia is usually self-limited; magnesium-containing agents should be limited or avoided in individuals with kidney disease. Magnesium excretion can be enhanced with saline diuresis. For more severe symptoms, intravenous calcium will antagonize the effects of magnesium.

KEY POINTS

- Early symptoms of hypermagnesemia include loss of deep tendon reflexes, progressing to flaccid paralysis at higher levels.
- For patients with hypermagnesemia, all magnesium-containing medications should be discontinued, and magnesium excretion can be enhanced with saline diuresis; for more severe symptoms, intravenous calcium will antagonize the effects of magnesium.

Acid-Base Disorders

Overview

Hydrogen ions are maintained within narrow limits and determine pH (**Table 7**). Any change in pH results in a predictable response to limit that change.

Causes of acid-base disorders can be determined by using blood gas pH, P_{CO_2}, serum bicarbonate measurements, and the serum anion gap. Arterial blood provides the most accurate measurement, although venous blood gases may be useful in following response to therapy. Venous gases are least useful in patients with shock, due to lower pH and higher P_{CO_2} values than in arterial gases.

Primary acid-base disorders are classified according to the underlying mechanism (metabolic or respiratory) and their effect on acid-base balance (acidosis or alkalosis) (**Figure 10**). Expected compensatory response to the primary disorder is then assessed (**Table 8**). A mixed acid-base disorder is present when measured values fall outside the range of the predicted compensatory response. The primary disorder is usually reflected by the blood pH, although a normal pH may occur in the context of a mixed disorder. Appropriate compensation may result in near-normal pH.

KEY POINTS

- Primary metabolic acidosis is defined by low serum bicarbonate and primary metabolic alkalosis by elevated serum bicarbonate.
- In primary respiratory acidosis, arterial P_{CO_2} is above normal; in primary respiratory alkalosis, P_{CO_2} is below normal.

TABLE 7. Physiologic Levels of Tests Used in the Assessment of Acid-Base Status

	pH	P_{CO_2}	Bicarbonate
Arterial blood	7.37-7.44	36-44 mm Hg (4.8-5.9 kPa)	22-26 mEq/L (22-26 mmol/L)
Venous blood	7.32-7.38	42-50 mm Hg (5.6-6.7 kPa)	23-27 mEq/L (23-27 mmol/L)

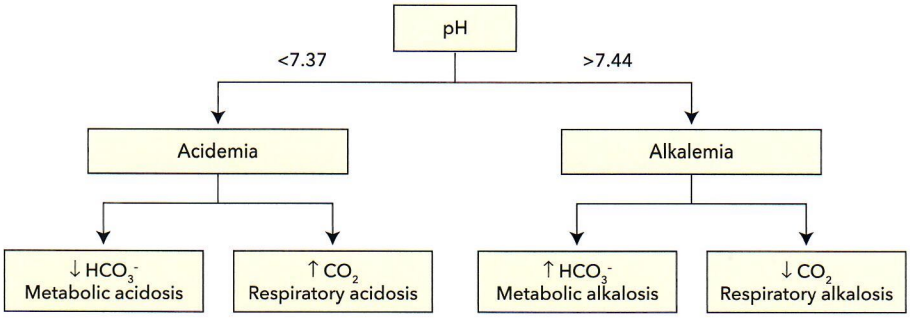


FIGURE 10. Classification of primary acid-base disorders.

Metabolic Acidosis

General Approach

A stepwise approach to assessment provides appropriate diagnosis of the underlying acid-base disorder. First, both pH and P_{CO_2} are needed to confirm the primary disorder because low serum bicarbonate may be a compensatory response to respiratory alkalosis.

Next, the serum anion gap is calculated to assess whether the low serum bicarbonate is due to loss of serum bicarbonate (no anion gap) or is a result of unmeasured anion (increased anion gap metabolic acidosis). The anion gap is calculated as follows:

Anion Gap = Serum Sodium (mEq/L) – (Serum Chloride [mEq/L] + Serum Bicarbonate [mEq/L])

The normal range for the anion gap is 8.0 to 10 mEq/L ± 2 mEq/L (8-10 mmol/L ± 2 mmol/L). In normal subjects, negatively charged albumin is a major contributor to the anion gap. Therefore, changes in albumin need to be taken into account. This is most important in the context of a low albumin wherein failure to correct the anion gap will result in underestimation of the true anion gap. The albumin-corrected anion gap (with normal albumin being 4.0 g/dL [40 g/L]) is calculated as follows:

Albumin-Corrected Anion Gap = Anion Gap + 2.5 × (Normal Albumin – Measured Albumin [g/dL])

If the corrected anion gap is increased, patients should next be assessed for coexistent normal anion gap acidosis or metabolic alkalosis. One method for detection of a coexistent additional acid-base disorder is to assess the ratio of the amount of anion gap abnormality (Δ anion gap) to the amount of bicarbonate abnormality (Δ bicarbonate), also known as the "delta-delta (Δ-Δ) ratio," as follows:

Δ–Δ Ratio = Δ Anion Gap/Δ Bicarbonate = (Anion Gap – 12)/(25 – Bicarbonate)

A Δ-Δ ratio of <0.5 to 1 may reflect the presence of concurrent normal anion gap metabolic acidosis; a ratio between 1 and 2 generally confirms the primary high anion gap metabolic acidosis; and a ratio of >2 may indicate the presence of metabolic alkalosis.

Patients with metabolic acidosis due to acute or chronic kidney disease may have either a normal anion gap (more modest disease) or an increased anion gap (more severe chronic kidney disease). When the glomerular filtration rate (GFR) decreases to <45 mL/min/1.73 m^2, decreased urine ammonium excretion leads to a normal anion gap metabolic acidosis, often associated with hyperkalemia. When the GFR decreases to <15 mL/min/1.73 m^2, retention of sulfates, phosphates, and organic acids results in an increased anion gap metabolic acidosis.

TABLE 8. Compensation in Acid-Base Disorders

Condition	Expected Compensation
Metabolic acidosis	Maximally compensated: expected P_{CO_2} = (1.5) [HCO_3] + 8 ± 2 (Winter's formula)
	Measured P_{CO_2} > expected: complicating primary respiratory acidosis
	Measured P_{CO_2} < expected: complicating primary respiratory alkalosis
Metabolic alkalosis	For each ↑ 1.0 mEq/L (1.0 mmol/L) in [HCO_3], P_{CO_2} ↑ 0.7 mm Hg (0.09 kPa)
Respiratory acidosis	Acute: 1.0 mEq/L (1.0 mmol/L) ↑ [HCO_3] for each 10 mm Hg (1.3 kPa) ↑ in P_{CO_2}
	Chronic: 3.5 mEq/L (3.5 mmol/L) ↑ [HCO_3] for each 10 mm Hg (1.3 kPa) ↑ in P_{CO_2}
	[HCO_3] < expected value: complicating metabolic acidosis
	[HCO_3] > expected value: complicating metabolic alkalosis
Respiratory alkalosis	Acute: 2.0 mEq/L (2.0 mmol/L) ↓ [HCO_3] for each 10 mm Hg (1.3 kPa) ↓ in P_{CO_2}
	Chronic: 4.0-5.0 mEq/L (4.0-5.0 mmol/L) ↓ [HCO_3] for each 10 mm Hg (1.3 kPa) ↓ in P_{CO_2}
	[HCO_3] < expected value: complicating metabolic acidosis
	[HCO_3] > expected value: complicating metabolic alkalosis

Most of the adverse effects that occur in patients with metabolic acidosis arise from the underlying cause rather than the low pH. But with severe acidosis, patients are susceptible to life-threatening arrhythmia and impaired cardiac function.

KEY POINTS

- The serum anion gap assesses whether the metabolic acidosis is due to an unmeasured organic anion (increased anion gap metabolic acidosis) or to a loss of bicarbonate (normal anion gap metabolic acidosis).
- In the presence of an increased anion gap metabolic acidosis, a delta-delta (Δ-Δ) ratio of <0.5 to 1 may indicate a concurrent normal anion gap metabolic acidosis, and a ratio of >2 may indicate a concurrent metabolic alkalosis.

Increased Anion Gap Metabolic Acidosis

Increased anion gap metabolic acidosis occurs when unmeasured anions accumulate. Lactic acidosis is the most common cause (**Table 9**). Less common causes include ketoacidosis (diabetic, alcoholic, or starvation), acute or chronic kidney injury, or poisoning (methanol, ethylene glycol, salicylate, or propylene glycol). The plasma osmolal gap may assist in identifying a cause. The plasma osmolal gap is the difference between the measured and calculated plasma osmolality. The calculated plasma osmolality is determined as follows:

$$\text{Plasma Osmolality (mOsm/kg } H_2O) = (2 \times \text{Serum Sodium [mEq/L]}) + \text{Plasma Glucose (mg/dL)}/18 + \text{Blood Urea Nitrogen (mg/dL)}/2.8$$

A high osmolal gap (>10 mOsm/kg H_2O) indicates the presence of unmeasured osmoles such as alcohol, methanol, or ethylene glycol, which are metabolized to organic acids, thereby increasing the anion gap. The patient's history should guide further testing for unmeasured anions.

Diabetic ketoacidosis usually presents with an increased anion gap metabolic acidosis due to accumulation of β-hydroxybutyrate and acetoacetate, although it may present with a normal anion gap due to excretion of ketoacids. Urine dipstick assays for ketones detect acetoacetate using the nitroprusside assay; however, β-hydroxybutyrate is the dominant ketoacid in diabetic ketoacidosis, so urine dipstick results can

TABLE 9. Causes of Lactic Acidosis

Condition	Cause	Clinical and Laboratory Manifestations	Treatment	Comments
Lactic Acidosis	**See below**	**Serum lactate level >4.0 mEq/L (4.0 mmol/L)**	**Treat underlying cause; sodium bicarbonate when arterial pH is <7.1 to raise to 7.2**	**Most common cause of increased anion gap metabolic acidosis**
Type A lactic acidosis	Tissue hypoperfusion	Multisystem organ dysfunction typically present	Correct cause of hypoperfusion	–
Type B lactic acidosis	Absent tissue hypoperfusion	Often related to drug/toxin-related impairment of metabolism	Discontinue/remove toxin	
Propofol	Propofol >4 mg/kg/h for >24 h	Rhabdomyolysis; hyperlipidemia; cardiogenic shock	Discontinue propofol; hemodialysis	Seen with continuous infusion, not bolus dosing
Metformin	Metformin use in patients with impaired kidney function	Most likely to occur in those with acute kidney injury	Hemodialysis	Contraindicated if eGFR <30 mL/min/1.73 m^2
HIV nucleoside reverse transcriptase inhibitor	Mitochondrial toxicity	Possible myopathy, peripheral neuropathy, hepatic steatosis	Discontinue medication; supportive care	Risk factors: female sex, pregnancy, obesity, poor liver function, lower CD4 count; mostly: ddI, d4T > AZT; rare: TFV, ABC, FTC, 3TC
Hematologic malignancy	Thought to be due to anaerobic metabolism in cancer cells	Hypoglycemia	Treat underlying malignancy	Portends very poor prognosis; seen in high-grade B-cell lymphomas
D-Lactic acidosis	Short-bowel syndrome[a]; undigested carbohydrates in the colon are metabolized to D-lactate by bacteria	Intermittent confusion; slurred speech; ataxia; increased anion gap metabolic acidosis with normal serum lactate level	Antibiotics (e.g., metronidazole or neomycin) directed toward bowel flora; restriction of dietary carbohydrates	Diagnosis requires measurement of D-lactate because D-isomer is not measured by conventional assays for serum lactate

3TC = lamivudine; ABC = abacavir; AZT = zidovudine; d4T = stavudine; ddI = didanosine; eGFR = estimated glomerular filtration rate; FTC = emtricitabine; TFV = tenofovir.

[a]After jejunoileal bypass or small-bowel resection.

be falsely negative or underestimate the total ketone load (see Clinical Evaluation of Kidney Function and MKSAP 19 Endocrinology and Metabolism).

Alcoholic ketoacidosis occurs in patients with chronic ethanol abuse who typically have a history of recent binge drinking, low caloric intake, and persistent vomiting. Treatment with intravenous saline and intravenous glucose typically results in rapid resolution of ketones due to induction of insulin secretion and suppression of glucagon release. For patients with chronic malnutrition related to alcohol use, thiamine should be administered before glucose to decrease the risk for precipitating Wernicke encephalopathy.

Medication and toxin exposures that cause increased anion gap metabolic acidosis are described in **Table 10**.

TABLE 10. Medication and Toxin Exposures that Cause Increased Anion Gap Metabolic Acidosis

Condition	Cause	Clinical and Laboratory Manifestations	Treatment	Comments
Ethylene glycol ingestion	Glycolic acid accumulation; calcium oxalate precipitation in renal tubules and crystals in the urine	AKI and flank pain due to precipitation of calcium oxalate in kidneys; hypocalcemic symptoms; cardiovascular collapse; pulmonary edema Serum bicarbonate level <10 mEq/L (10 mmol/L); plasma osmolal gap >10 mOsm/kg H_2O	Fomepizole IV hydration Hemodialysis: in severe acidemia, very large ingestions, severe CNS depression, AKI, systemic collapse Pyridoxine and thiamine: in suspected ethylene glycol toxicity Sodium bicarbonate	Found in antifreeze, solvents, cosmetics May be difficult to differentiate from methanol ingestion
Methanol ingestion	Formic acid accumulation	CNS damage; optic nerve/eye damage with blindness; papilledema; mydriasis; afferent pupillary defect; abdominal pain; pancreatitis Serum bicarbonate level <10 mEq/L (10 mmol/L); plasma osmolal gap >10 mOsm/kg H_2O	Fomepizole Hemodialysis: in severe acidemia, very large ingestions, severe CNS depression, any visual impairment Folic acid: in suspected methanol toxicity Sodium bicarbonate	Found in windshield-washing fluid, commercial solvents, paints, some antifreezes May be difficult to differentiate from ethylene glycol ingestion 80%-90% mortality rate with methanol ingestion; permanent blindness may occur
Salicylate toxicity	Salicylate anion accumulation; ingestion of as little as 10 grams of aspirin in adults	Respiratory alkalosis; tinnitus; nausea/vomiting; impaired mental status; cerebral edema and brainstem herniation; tachypnea; noncardiogenic pulmonary edema; hepatic injury; lactic acidosis or ketoacidosis with severe intoxication	Bicarbonate infusion: alkalinization mitigates CNS toxicity; aim for urine pH >7.5 Hemodialysis: in AKI, impaired mental status, cerebral edema, serum salicylate levels >100 mg/dL with acute ingestion and levels >60 mg/dL with chronic ingestion, refractory acidemia, pulmonary edema	Toxicity can develop from ingestion or mucocutaneous exposure to salicylate preparations such as methyl salicylate (oil of wintergreen)
Propylene glycol toxicity	Large doses of propylene glycol (a solvent used for IV medications), most commonly lorazepam diluted in propylene glycol (80%)	AKI; anion gap metabolic acidosis with increased plasma osmolal gap; toxicity when propylene glycol levels >25 mg/dL or plasma osmolal gap >10 mOsm/kg H_2O	Discontinue infusion Hemodialysis	Monitor acid-base status and serum osmolality when lorazepam doses >1 mg/kg/d; unlikely to develop if 24-h lorazepam dose is limited to <166 mg/d
Pyroglutamic (5-oxoproline) acidosis	Chronic acetaminophen ingestion; most common in critically ill patients, those with poor nutrition, liver disease, or CKD, and in vegetarians	Impaired mental status; on urine testing for organic anions, high concentrations of urine pyroglutamate (5-oxoproline)	Discontinue acetaminophen Consider *N*-acetylcysteine to regenerate depleted glutathione stores	Female preponderance (80%); genetic factors may play a role

AKI = acute kidney injury; CKD = chronic kidney disease; CNS = central nervous system; IV = intravenous.

KEY POINTS

- Lactic acidosis is the most common cause of increased anion gap metabolic acidosis.
- Ethylene glycol or methanol ingestion should be suspected in patients with an increased anion gap metabolic acidosis associated with a serum bicarbonate level <10 mEq/L (10 mmol/L) and a plasma osmolal gap >10 mOsm/kg H_2O.

Normal Anion Gap Metabolic Acidosis

Normal anion gap metabolic acidoses most often result from gastrointestinal bicarbonate losses (diarrhea), kidney bicarbonate losses (type 2 renal tubular acidosis), or inability of the kidney to adequately excrete acid (types 1 and 4 renal tubular acidosis; chronic kidney disease). Although a patient history may elucidate the cause, the urine anion gap may help to narrow down the cause.

In response to acidemia, the kidneys should increase acid excretion. This is achieved primarily by increased tubular production of ammonia (NH_3) and secretion of protons, resulting in increased urine ammonium (NH_4^+). The amount of urine ammonium reflects the ability of the kidneys to respond appropriately to acidemia and indicates if the kidney is a cause of the acidosis. Because urine ammonium is difficult to measure, the urine anion gap is used as a surrogate to assess kidney acid excretion:

$$\text{Urine Anion Gap} = (\text{Urine Sodium} + \text{Urine Potassium}) - \text{Urine Chloride}$$

In patients with gastrointestinal losses of bicarbonate (diarrhea; laxative abuse) or those exposed to an acid load, urine NH_4^+ should increase. Ammonium cation excretion results in proportionately less excretion of sodium and potassium (the predominant urine cations). Chloride anion excretion continues with ammonium cation excretion to maintain electrical neutrality. In the context of increased urine NH_4^+ production, therefore, the urine anion gap will be negative (less than zero). A positive urine anion gap in a patient with acidemia suggests the presence of a distal renal tubular acidosis. Proton secretion in the distal nephron generates NH_4^+, and in distal renal tubular acidosis there is a defect in this proton secretion. Therefore, urine NH_4^+ will be low, with proportionately greater sodium and potassium excretion resulting in a positive urine anion gap.

The urine anion gap, together with serum potassium levels and urine pH, can help further distinguish the causes of normal anion gap metabolic acidosis (**Table 11**).

Type 2 (Proximal) Renal Tubular Acidosis

The primary defect in type 2 (proximal) renal tubular acidosis (RTA) is failure of the proximal tubule to adequately absorb filtered bicarbonate, resulting in bicarbonate loss and acidosis. Type 2 RTA is usually accompanied by other evidence of proximal tubular dysfunction, including complete or partial Fanconi syndrome (glycosuria, phosphaturia, aminoaciduria, hypouricemia). As blood bicarbonate levels decrease, less bicarbonate is filtered and eventually the resorptive threshold is reached, such that serum bicarbonate levels stabilize (around 12-14 mEq/L [12-14 mmol/L]). Because the distal nephron functions appropriately in type 2 RTA, urine can still be acidified to a pH <5.5 and NH_4^+ production will be normal, usually making the urine anion gap negative. Hypokalemia is also often present due to increased distal tubular potassium secretion. This occurs because sodium accompanies bicarbonate to the distal tubule, where sodium is reabsorbed in exchange for potassium.

The most common causes of type 2 RTA include myeloma light chains as well as nephrotoxic medications such as ifosfamide, carbonic anhydrase inhibitors (acetazolamide and topiramate), and tenofovir disoproxil fumarate (although toxicity is much less likely with tenofovir alafenamide).

Alkali replacement is the mainstay of treatment for type 2 RTA. Thiazide diuretics may help by causing mild volume depletion with subsequent aldosterone-driven proximal reabsorption of sodium and bicarbonate.

Type 1 (Hypokalemic Distal) Renal Tubular Acidosis

In type 1 (hypokalemic distal) RTA, a distal tubular defect results in impaired excretion of hydrogen ions by the distal nephron (hence, low urine ammonium and positive urine anion gap) with inability to acidify urine below a pH of 6.0. Serum bicarbonate may fall below 10 mEq/L (10 mmol/L) as levels fail to stabilize as is seen with type 2 (proximal) RTA;

TABLE 11. Diagnostic Approach to Normal Anion Gap Metabolic Acidosis

Diagnosis	Urine Anion Gap ($U_{Na} + U_K) - U_{Cl}$	Serum Potassium	Urine pH
Ammonium chloride ingestion (acid load)	Negative	Normal	<5.5
Diarrhea and acidosis	Negative	Normal	<5.5
Type 2 (proximal) RTA[a]	Negative	Decreased	Variable[b]
Type 1 (hypokalemic distal) RTA	Positive	Decreased	>5.5
Type 4 (hyperkalemic distal) RTA	Positive	Increased	<5.5

RTA = renal tubular acidosis; U_{Cl} = urine chloride; U_K = urine potassium; U_{Na} = urine sodium.

[a]Type 2 (proximal) RTA is often associated with Fanconi or partial Fanconi syndrome (glycosuria, phosphaturia, aminoaciduria, hypouricemia).

[b]Patients with type 2 (proximal) RTA have normal distal renal tubular function and can acidify the urine after the serum bicarbonate decreases to a point at which the filtered load of bicarbonate can be normally reabsorbed.

despite lower filtered bicarbonate, continued impairment in acid excretion will worsen the acidosis.

The most common causes include Sjögren syndrome and other tubulointerstitial diseases, including reflux uropathy and obstructive uropathy. Type 1 RTA can also be caused by medications such as amphotericin B and lithium and has been described in dysproteinemias, sickle cell disease, and Wilson disease.

Urinary potassium wasting in the setting of diminished proton secretion underlies the development of hypokalemia. Hypercalciuria and hyperphosphatemia are frequent in untreated type 1 RTA because of increased calcium and phosphate release from bone due to buffering of acid. Reduced tubular calcium resorption in the context of acidosis exacerbates hypercalciuria. Increased proximal reabsorption of citrate in the context of acidosis and hypokalemia causes hypocitraturia. Citrate usually inhibits calcium crystallization; therefore, hypocitraturia, in addition to hypercalciuria, increases the risk for calcium phosphate stones and nephrocalcinosis.

Treatment consists of potassium citrate (citrate is metabolized to bicarbonate), with the dose titrated to response.

Type 4 (Hyperkalemic Distal) Renal Tubular Acidosis

Type 4 (hyperkalemic distal) RTA is caused by aldosterone deficiency or resistance. Primary adrenal insufficiency (Addison disease) may cause aldosterone deficiency. Hyporeninemic hypoaldosteronism is a more common cause and may occur in the presence of various kidney diseases, most often diabetic kidney disease. Aldosterone resistance can occur in those with tubulointerstitial disease, including urinary obstruction, sickle cell disease, medullary cystic kidney disease, and kidney transplant rejection. Drug-induced type 4 RTA can be caused by numerous drugs that reduce aldosterone production, including ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors, heparin, and cyclooxygenase-2 inhibitors.

Type 4 RTA is associated with a positive urine anion gap but a urine pH <5.5 (see Table 11). Hyperkalemia decreases NH_3 production (and therefore NH_4^+), resulting in a positive urine anion gap. Even if the distal nephron is able to decrease urine pH appropriately, reduced NH_4^+ excretion will lead to insufficient acid excretion, generating a metabolic acidosis.

Treatment is focused on correcting the underlying cause if possible; offending medications should be discontinued when identified. Because many patients are also hypertensive and volume expanded, thiazide or loop diuretics may help increase serum bicarbonate and decrease serum potassium. Fludrocortisone can be used to replace mineralocorticoids in hyporeninemic hypoaldosteronism in those without hypertension or heart failure.

Mixed Forms of Renal Tubular Acidosis

Topiramate may cause mixed RTA through inhibition of carbonic anhydrase in both proximal and distal tubules. Because of consequent high urine pH (>6.0) and hypocitraturia, topiramate is associated with increased risk for calcium phosphate stones. Rare hereditary carbonic anhydrase deficiencies also result in combined mixed RTA.

KEY POINTS

- In normal anion gap metabolic acidosis, a negative urine anion gap identifies a nonrenal cause, whereas a positive urine anion gap is associated with distal renal tubular acidoses.
- In type 2 (proximal) renal tubular acidosis, failure of the proximal tubule to adequately absorb filtered bicarbonate causes bicarbonate loss; treatment consists of alkali replacement and a thiazide diuretic.
- In type 1 (hypokalemic distal) renal tubular acidosis, impaired distal hydrogen ion excretion causes citrate reabsorption and increases the risk for nephrocalcinosis; treatment consists of potassium citrate.
- In type 4 (hyperkalemic distal) renal tubular acidosis, aldosterone deficiency or resistance causes hyperkalemia and decreased NH_4^+ excretion; treatment includes correction of the underlying cause and treatment of hyperkalemia.

Metabolic Alkalosis

Metabolic alkalosis results either from a loss of acid or from administration or retention of bicarbonate (alkali). Metabolic alkalosis occurs in two phases: a generation phase in which the primary disorder (such as vomiting or the accumulation of alkali) occurs, and a maintenance phase in which typical renal compensatory excretion of excess bicarbonate is ineffective. The generation phase usually involves the gastrointestinal (GI) tract (in vomiting-induced acid loss) or the kidney (typically a mineralocorticoid effect, either primary or in response to intravascular volume depletion, with resulting sodium and bicarbonate retention at the expense of acid and potassium secretion). Conditions that contribute to maintenance of metabolic alkalosis include volume contraction, ineffective arterial blood volume (e.g., in cirrhosis or heart failure), hypokalemia, chloride depletion, hyperaldosteronism, and decreased glomerular filtration.

Symptoms of metabolic alkalosis are usually related to the underlying disorder. Coexisting hypokalemia markedly increases the risk for cardiac arrhythmias. Severe metabolic alkalosis (serum bicarbonate >50 mEq/L [50 mmol/L]) can cause hypocalcemia, hypoventilation, and hypoxemia, with seizures, delirium, and stupor.

Thorough history and physical examination, including assessment of blood pressure and volume status, are essential to identifying the likely cause (**Figure 11**). Laboratory evaluation is based on urine chloride rather than urine sodium.

The most common causes of metabolic alkalosis are associated with chloride depletion: vomiting, nasogastric suction,

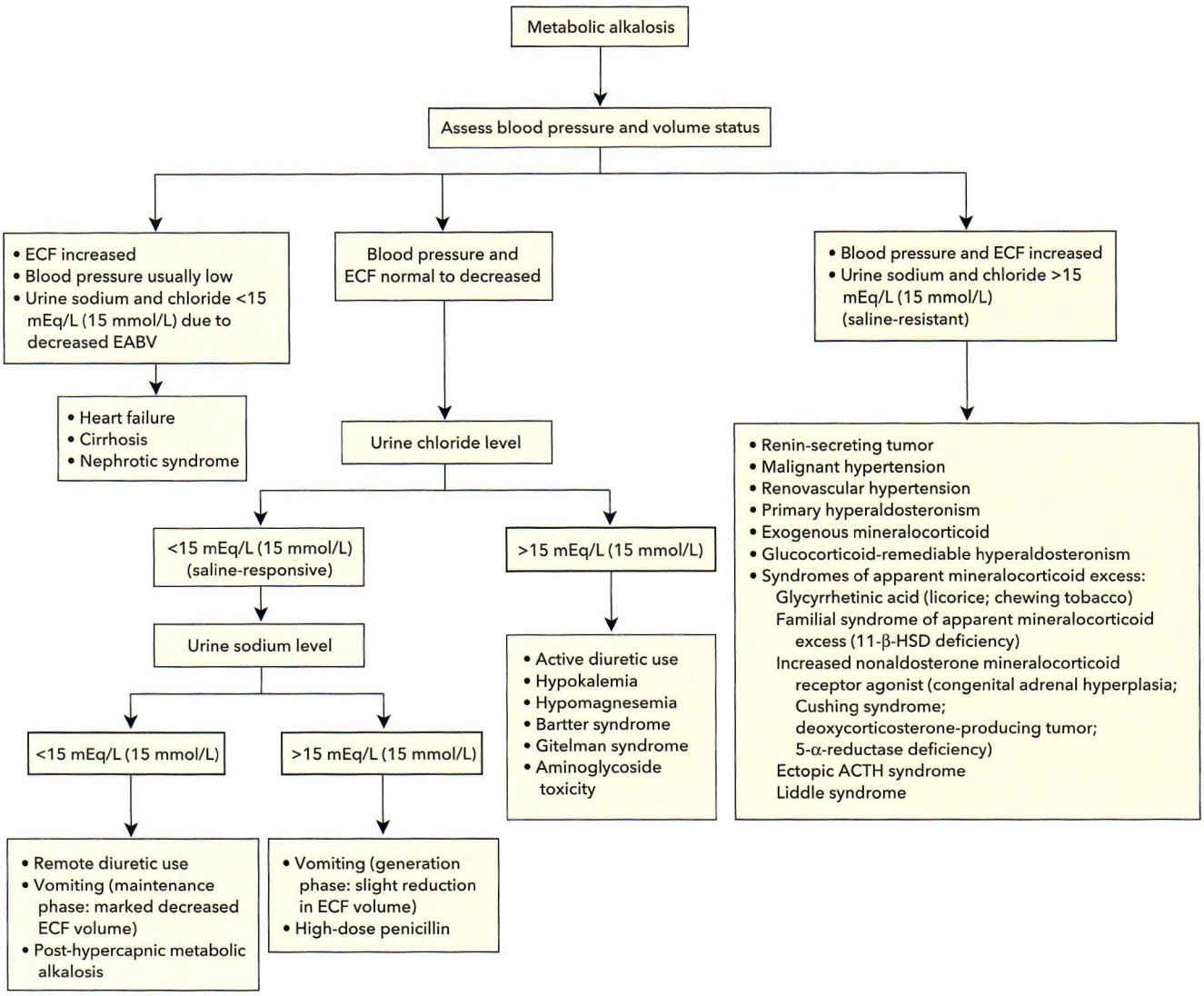


FIGURE 11. Assessment of metabolic alkalosis. ACTH = adrenocorticotropic hormone; EABV = effective arterial blood volume; ECF = extracellular fluid; HSD = hydroxysteroid dehydrogenase.

and diuretic use. Although upper GI losses are far more common, lower GI chloride-secretory diarrheas (villous adenoma, congenital chloridorrhea) can rarely cause chloride depletion with bicarbonate retention. A "contraction alkalosis" results from loss of extracellular fluid containing low amounts of bicarbonate, leaving a contracted extracellular volume containing a constant amount of existing circulating bicarbonate.

In patients with low urine chloride (<15 mEq/L [15 mmol/L]), normal/low intravascular volume, and normal/low extracellular volume, treatment consists of saline administration plus repletion of potassium (saline-responsive metabolic alkalosis) while addressing the primary cause of the alkalosis. In contrast, those with a low urine chloride (<15 mEq/L [15 mmol/L]) and normal/low intravascular volume but with an increased extravascular volume (heart failure, cirrhosis) have secondary hyperaldosteronism with sodium and bicarbonate retention manifested by edema; treatment is tailored to improving effective arterial blood volume and diuresis.

Mineralocorticoid excess presents with a high urine chloride (>15 mEq/L [15 mmol/L]) with elevated blood pressure and hypokalemia without volume overload (saline-resistant metabolic alkalosis). The lack of an overt increase in extravascular volume is often described as "aldosterone escape": After initial sodium retention, sodium balance is attained through spontaneous diuresis that returns vascular volume toward normal. Mineralocorticoid excess is treated with potassium repletion and treatment of the underlying condition.

Rarely, patients may have clinical features consistent with saline-responsive metabolic alkalosis but with a urine chloride of >15 mEq/L (15 mmol/L); ongoing diuretic use can present this way. Two autosomal recessive genetic conditions, Bartter and Gitelman syndromes, result in disordered renal sodium

and chloride transporters and clinically mimic loop diuretic and thiazide diuretic use, respectively. These diagnoses should be considered only after urine diuretic screening.

KEY POINTS

- The most common causes of metabolic alkalosis are associated with low urine chloride and chloride depletion (vomiting, nasogastric suction, and diuretic use).
- Metabolic alkalosis from mineralocorticoid excess presents with hypertension, hypokalemia, euvolemia, and an elevated urine chloride.
- Patients with metabolic alkalosis, volume overload, and a low urine chloride usually have low effective arterial blood volume from cirrhosis or heart failure.

Respiratory Acidosis

Respiratory acidosis is characterized by retention of arterial CO_2. The most common causes are impaired arterial-alveolar gas exchange (pneumonia, pulmonary edema, interstitial lung diseases), airway obstruction (COPD, status asthmaticus, upper airway obstruction), disordered regulation of ventilation (central or obstructive sleep apnea), or inadequate ventilation (musculoskeletal disease, neuromuscular disorders).

With acute respiratory acidosis, excess CO_2 is initially buffered by water, leading to formation of hydrogen ions and bicarbonate. Thus, the acute arterial blood gas reveals increased P_{CO_2}, decreased pH, and a slight increase in bicarbonate. Over 3 to 5 days, compensatory increases in renal acid excretion (with bicarbonate reabsorption) reach a new steady state (see Table 7).

Clinical manifestations of respiratory acidosis are complicated by frequently associated hypoxemia. Symptoms are predominantly neurologic, including headache, anxiety, blurred vision, and tremor. Severe acidosis can cause confusion, somnolence, or seizures. Chronic respiratory acidosis may have milder neurologic effects such as memory loss, inattentiveness, or irritability. Cardiovascular manifestations include vasodilation and tachycardia that may evolve to cardiac arrhythmias and decreased cardiac output.

Treatment involves correcting the underlying mechanism if possible and may necessitate mechanical ventilation to reduce CO_2 and oxygen supplementation.

KEY POINT

- In respiratory acidosis, arterial blood gases demonstrate elevated P_{CO_2} (hypercapnia), decreased pH, and increased bicarbonate.

Respiratory Alkalosis

Respiratory alkalosis is defined by a reduction in arterial P_{CO_2} due to increased ventilation. The most common causes are an enhanced respiratory drive (sepsis, hepatic failure, anxiety, iatrogenic hyperventilation, pregnancy, nicotine, salicylate intoxication, subarachnoid hemorrhage), hypoxemia, and pulmonary disease with stimulation of thoracic stretch receptors (pneumonia, acute respiratory distress syndrome, pulmonary embolism).

Acute hypocapnia leads to a rapid increase in arterial pH. However, immediate compensatory diffusion of hydrogen ions from intracellular stores, and subsequent reduction in serum bicarbonate through regeneration of CO_2, limits the magnitude of alkalosis. The typical arterial blood gas in this setting demonstrates a decrease in P_{CO_2}, an increase in pH, and a slight decrease in bicarbonate. Over 2 to 3 days, bicarbonate levels decrease further as compensatory kidney excretion of bicarbonate reaches a new steady state (see Table 8).

Respiratory alkalosis may cause increased cellular lactic acid production. Increases in negatively charged albumin may cause a mildly increased anion gap and decreased ionized calcium (from enhanced albumin binding). Finally, severe hypophosphatemia can occur due to a shift of phosphate from extracellular to intracellular fluid.

Clinical presentation includes underlying tachypnea and neurologic findings such as lightheadedness, numbness and paresthesia, cramps, confusion, and, rarely, seizures. An important consideration is salicylate intoxication, which in its early phases presents as respiratory alkalosis and an increased anion gap metabolic acidosis with mental status changes.

Treatment is directed at correction of the primary disorder. Treatment of salicylate intoxication includes forced diuresis, urine alkalization, or hemodialysis. For anxiety-induced or psychogenic hyperventilation, increasing inspired P_{CO_2} by closed bag rebreathing may be effective. In rare circumstances of severe alkalemia (pH >7.55) with hemodynamic instability, arrhythmias, or altered mental status, strategies to reduce bicarbonate include acetazolamide or controlled mechanical hypoventilation.

KEY POINTS

- Respiratory alkalosis is associated with a decrease in P_{CO_2}, an increase in pH, and a slight decrease in bicarbonate.
- Salicylate intoxication presents in its early phase as respiratory alkalosis and an increased anion gap metabolic acidosis.

Hypertension

Epidemiology

In the United States, hypertension is second only to smoking as a risk factor for death and disability. Hypertension is also one of the leading risk factors for cardiovascular death and disability worldwide. The prevalence of hypertension varies based on the designated cut-point, increasing from 32% to 46% when the cutoff is changed from a blood pressure (BP)

≥140/90 mm Hg to ≥130/80 mm Hg. Prevalence increases as the population ages. Overall, persons free of hypertension at 55 years of age still have a 90% lifetime risk for developing hypertension. Although several clinical trials revealed that treatment of hypertension with medication reduces cardiovascular events, hypertension control to a BP <140/90 mm Hg is achieved in only 50% of the U.S. population.

Consequences of Sustained Hypertension

End-Organ Injury

Either acute (hypertensive emergency) or chronic elevation in BP may lead to end-organ damage.

Eye

Chronic elevation of BP can lead to elevated arteriolar pressure, resulting in hypertensive retinopathy, which manifests as vasoconstriction and arteriolar narrowing (arteriovenous nicking or copper wiring on funduscopic examination), endothelial damage, and retinal hemorrhage (flame hemorrhages) (**Figure 12**). Optic neuropathy may result from ischemia to the nerve fiber secondary to fibrinoid necrosis of vessels, manifesting as cotton wool spots or optic disc pallor.

Hypertensive emergency can lead to papilledema, resulting from leakage, ischemia, and fibrinoid necrosis of arterioles supplying the optic disc, causing optic nerve hemorrhage and swelling. Loss of visual acuity and blindness can occur.

Medium to Large Blood Vessels

Long-standing hypertension can damage the vascular endothelium and, combined with elevated cholesterol and especially in the presence of diabetes mellitus, lead to peripheral vascular disease, including aortic aneurysm.

Hypertensive emergency may cause aortic aneurysmal rupture or aortic wall dissection.

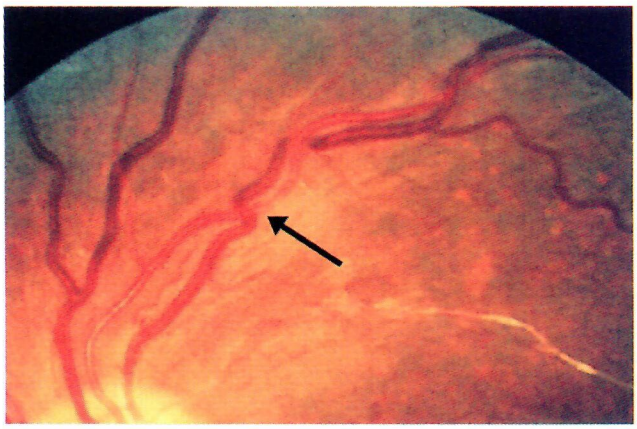


FIGURE 12. Changes of arteriosclerosis characterized by arteriovenous nicking, defined as disappearance of a short segment of the venule where it is crossed by the arteriole (*arrow*) and 90-degree angle crossing of the arterioles and venules.

Brain

Hypertension is the most important risk factor that accounts for 50% of transient ischemic attacks, lacunar infarction, and other stroke subtypes. Hypertension is also associated with vascular neurocognitive disorder.

Hypertensive emergency has serious manifestations such as hemorrhagic stroke or subarachnoid hemorrhage from cerebral aneurysmal rupture.

Heart

Hypertension is a major risk factor for acute coronary syndrome, myocardial infarction, and both diastolic and systolic heart failure.

Kidney

Injury to the renal vasculature results in arteriosclerosis and atherosclerosis and, ultimately, hypertensive nephrosclerosis and chronic kidney disease (CKD). Hypertension is a major cause of CKD and end-stage kidney disease (ESKD), especially in Black persons. Additionally, uncontrolled hypertension can increase the rate of CKD progression in patients with other underlying CKD causes, such as diabetic kidney disease.

Hypertensive emergency can cause acute kidney injury (AKI), with arteriolar proliferation (onion skinning), fibrinoid necrosis, and features of thrombotic microangiopathy.

Clinical Impact

Hypertension is one of the most significant but modifiable risk factors for cardiovascular disease, stroke, ESKD, and overall mortality. Systolic is more important than diastolic BP as an independent risk factor for coronary events, heart failure, stroke, and ESKD. Data suggest that BP-related cardiovascular disease, kidney disease, and risk for vascular death are evident before development of hypertension per se; risk increases progressively throughout ranges of BP that were previously recognized as normal and are now referred to as "elevated blood pressure." Therefore, a large proportion of the U.S. population has BP below the traditional threshold for pharmacologic treatment but high enough to signify future risk.

KEY POINT

- Either acute (hypertensive emergency) or chronic elevation of blood pressure can lead to significant injury in multiple organs, including the eyes, blood vessels, brain, heart, and kidneys.

Blood Pressure Measurement

Proper Technique

The calculated average of repeat BP measurements using proper technique is necessary for clinical management. Smoking, caffeinated beverages, or exercise within 30 minutes before measurements should be avoided. A properly calibrated

and validated instrument should be employed. BP should be measured in both arms during the first visit, and the arm with the higher value should be used to measure BP during subsequent visits. The patient should be seated, not talking, in a chair for ≥3 to 5 minutes, with the back supported, feet on the floor, legs uncrossed, and the arm bared and supported on a flat surface at the level of the right atrium. The cuff size should be chosen to ensure that the bladder encircles ≥80% of the upper arm. Using a cuff that is too small will result in an artificially elevated reading, and using a cuff that is too large will result in an artificially lower reading. At least two measurements should be taken and averaged, approximately 2 minutes apart; the process should be repeated if the initial measurements differ by >5 mm Hg.

Auscultatory Blood Pressure Monitoring

The sphygmomanometer bladder is placed on the bare arm over the pulsation of the brachial artery, with the edge of the lower cuff approximately 2 to 3 cm above the antecubital fossa. A stethoscope is placed over the brachial artery in the antecubital fossa. The cuff is inflated ≥30 mm Hg above the point at which the palpated brachial pulse disappears (estimated systolic BP), then deflated at a rate of 2 mm Hg per second. Systolic BP is recorded at the point at which the first sound is heard (onset of the first Korotkoff sound), and diastolic BP is recorded at the point the sound disappears (disappearance of all Korotkoff sounds).

Automated Blood Pressure Monitoring

Fully automated devices using the oscillometric method may reduce human error and may be preferred for use in clinical practice. These devices can take multiple readings without the presence of an observer and may provide more accurate BP measurements than auscultation. Proper calibration is essential for accuracy. BP measured with automated devices versus the auscultatory method has been shown to be closer to awake out-of-office BP levels measured with ambulatory BP monitoring and may have a stronger association with subclinical cardiovascular disease.

The American Heart Association recommends the use of a validated, automated office BP device as the preferred approach for evaluating office BP. Three separate automated measurements, optimally taken when the patient is unattended, should be averaged to obtain the final BP reading.

Out-of-Office Blood Pressure Monitoring

Ambulatory Blood Pressure Monitoring

Ambulatory BP monitoring (ABPM) using an electronic BP measuring device is the gold standard for the assessment of BP out of the office and is a better predictor of cardiovascular outcomes, including left ventricular hypertrophy and cardiac death, compared with office-based measurements. The device can be worn continuously for periods of 24 hours or longer and is programmed to measure and record BP every 15 to 60 minutes. Normal BP by ABPM includes a 24-hour average BP <115/75 mm Hg, daytime average BP <120/80 mm Hg, and nighttime average BP <100/65 mm Hg. ABPM provides valuable information supplementary to office BP in the evaluation of conditions, including the following:

- Suspected white coat hypertension (BP measures higher in the office)
- Suspected masked hypertension (BP measures lower in the office)
- Suspected episodic hypertension
- Apparent treatment-resistant hypertension
- Hypotensive symptoms with antihypertensive medication treatment
- Autonomic dysfunction
- Possible nondipping (<10% nocturnal decrease in BP, which is associated with increased risk for cardiovascular events)

Home Blood Pressure Monitoring

Home BP monitoring refers to the measurement of BP at home by the patient, often by using an electronic BP device, and is an alternative for the measurement of out-of-office BP when ABPM is not available or tolerable by the patient. Observational data show that average home systolic and diastolic BP measurements are more predictive of cardiovascular death than office readings, but less predictive than ABPM average readings. The advantage of home BP monitoring over ABPM is that home monitoring is more readily available, less expensive, and less time consuming. In addition, home BP monitoring encourages patient adherence to lifestyle modifications and antihypertensive medications. However, unlike ABPM, which provides information regarding continuous BP measurements during awake, asleep, and exertion periods, home BP measurements can only be taken during awake hours and when the patient is at rest.

To ensure the most accurate BP measurements at home, upper arm cuffs are preferred over newer devices that measure BP more distally, such as at the wrist, given that systolic BP is higher and diastolic lower in distal arteries. Finger measurements are generally not accurate. In addition, patients should be educated on the proper measurement technique, frequency and timing of measurements, and avoidance of self-adjustment of antihypertensive medications based on home BP. BP readings and times of measurement should be recorded, and a running list brought to office visits for assistance with management. The device should be brought to the office initially and periodically to validate accuracy of readings. Hypertension is defined as home BP monitoring measurements that average ≥130/80 mm Hg.

Other Blood Pressure Monitoring Approaches

With increased access to technology and interest in telehealth, new approaches for measurement of BP outside of the office

TABLE 12. Definitions of Blood Pressure for Adults

Definitions[a]	Office-Based Readings (mm Hg)[a]	24-Hour Ambulatory Readings (mm Hg)[b]	Self-Recorded Readings (mm Hg)[b]
Normal	<120/80	<115/75	<120/80
Elevated Blood Pressure	120-129/<80	–	–
Hypertension, Stage 1	130-139/80-89	≥125/75	≥130/80
Hypertension, Stage 2	≥140/90	≥130/80	≥135/85
White Coat Hypertension	>130/80	<125/75	<130/80
Masked Hypertension	<130/80	≥125/75	≥130/80

[a]Based on Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e127-e248. [PMID: 29146535] doi:10.1016/j.jacc.2017.11.006

[b]The corresponding thresholds of 24-hour ambulatory and self-recorded home blood pressure readings are provided as a guide and should be interpreted with caution, given that they are based on European, Australian, and Asian populations, with few available data in U.S. populations.

include pharmacist-measured BP, BP kiosks (self-contained stations for measuring BP in otherwise public areas, such as supermarkets or airports), and wearable devices, which can raise patient awareness and possibly improve adherence. However, given the potential lack of device calibration and validation, more studies are needed before these measures can be substituted for ABPM and home BP measurements in practice.

KEY POINTS

- Ambulatory blood pressure monitoring is a better predictor of cardiovascular outcomes, including left ventricular hypertrophy and cardiac death, compared with office-based blood pressure measurements.
- Normal blood pressure by ambulatory blood pressure measurement includes a 24-hour average blood pressure <115/75 mm Hg, daytime average blood pressure <120/80 mm Hg, and nighttime average BP <100/65 mm Hg.
- Home blood pressure monitoring is an acceptable alternative if ambulatory blood pressure monitoring is not available or tolerable by the patient.

Definitions

The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) BP guideline provides BP definitions and recommendations. Hypertension is defined as BP ≥130/80 mm Hg. Additional definitions of BP are listed in **Table 12**.

Screening and Diagnosis

The U.S. Preventive Services Task Force (USPSTF) recommends screening for hypertension in adults ≥18 years of age to identify those at increased risk for cardiovascular disease from hypertension and to begin early interventions to decrease this risk. Adults aged 18 to 39 years with a BP <130/85 mm Hg and without cardiovascular risk factors should be rescreened every 3 to 5 years. Those aged ≥40 years and persons at increased risk for hypertension (e.g., those who have BP of 130-139/85-89 mm Hg, are overweight, or are Black) should be screened annually. The ACC/AHA recommends that adults with an elevated BP (120-129/<80 mm Hg) or stage 1 hypertension (130-139/80-89 mm Hg) who are not yet on therapy have their BP repeated within 3 to 6 months.

A diagnosis of hypertension (BP ≥130/80 mm Hg) should be based on an average of two or more elevated systolic and/or diastolic BP measurements obtained on two or more occasions. Out-of-office ABPM or home BP monitoring of BP measurements is recommended to confirm hypertension. Compared with a single measurement, multiple measurements over time have better positive predictive values for hypertension diagnosis. Evidence regarding the prevalence of white coat hypertension supports confirming elevated BP with 24-hour ABPM or home BP monitoring before initiating treatment.

KEY POINTS

- The U.S. Preventive Services Task Force recommends screening for hypertension in adults ≥18 years of age to identify those at increased risk for cardiovascular disease from hypertension and to begin early interventions to decrease this risk.
- The American College of Cardiology/American Heart Association guideline recommends that patients with elevated blood pressure or stage 1 hypertension who are not yet on therapy have repeat BP assessment in 3 to 6 months.
- A diagnosis of hypertension should be based on an average of two or more elevated systolic and/or diastolic blood pressure measurements obtained on two or more occasions; obtaining measurements outside of the clinical setting for diagnostic confirmation is recommended before starting treatment.

Evaluation of the Patient with Newly Diagnosed Hypertension

Initial evaluation of a patient with newly diagnosed hypertension includes a complete history, physical examination, and screening laboratory studies to address the following:

- Establish whether a familial pattern of hypertension is present.
- Rule out secondary, potentially reversible, causes.
- Identify and eliminate modifiable factors that can elevate BP.
- Assess for the presence of other cardiovascular risk factors.
- Assess for end-organ damage.
- Identify potential barriers to lifestyle modification for lowering BP.

History

A complete history should be elicited to identify a personal history of the following: stroke or myocardial infarction, thyroid disease, kidney disease, obstructive sleep apnea, and additional cardiovascular risk factors. Family history should be explored for a genetic pattern of hypertension and premature cardiovascular disease.

A complete review of the systems is warranted, especially to elicit the presence of episodic palpitations, headaches, or sweating (which may suggest pheochromocytoma); visual changes (to assess end-organ damage); or gross hematuria (which may suggest underlying kidney disease). Behavioral and psychosocial contributors to hypertension, including a sedentary routine, illicit drug use, excessive alcohol, tobacco smoking, and high dietary sodium intake should also be explored.

A complete list of prescription and nonprescription medications, including complementary and alternative medications (herbal supplements) and illicit drugs, is of utmost importance because many medications can result in reversible BP elevations (**Table 13**). If the patient is taking any drugs that may result in BP elevation, the drug should be discontinued and BP remeasured in 1 month.

Physical Examination

Physical examination should focus on the following:

- Measure BP accurately in both arms.
- Measure body weight and calculate BMI to ascertain cardiovascular risk.
- Recognize target organ damage: eye examination (retinopathy or papilledema); volume status (elevated jugular venous pressure or lower extremity edema suggesting heart failure or CKD); peripheral vascular examination (unequal pulses, carotid or abdominal bruits suggesting vascular disease); cardiac examination (laterally displaced point of maximal impulse, left ventricular enlargement, or S_4 gallop suggestive of left ventricular hypertrophy or fibrosis).

TABLE 13. Drugs That Can Raise Blood Pressure

Drug/Drug Class	Potential Mechanisms
Prescription Drugs	
Antidepressants: monoamine oxidase inhibitors; selective serotonin reuptake inhibitors; serotonin-norepinephrine reuptake inhibitors	Adrenergic stimulation
Calcineurin inhibitors: cyclosporine A; tacrolimus	Vasoconstriction; sympathetic excitation; sodium retention
Contraceptives: estrogens; progesterones	Sodium retention; increased renin-angiotensin system activity
Glucocorticoids	Sodium retention; weight gain
Erythropoietin-stimulating agents	Vasoconstriction
NSAIDs	Sodium retention
Sympathomimetics (methylphenidate)	Adrenergic stimulation
Vascular endothelial growth factor antagonists	Endothelial dysfunction; vasoconstriction
Nonprescription Drugs	
Anabolic steroids	Sodium retention
Caffeine	Adrenergic stimulation
Ethanol	Adrenergic stimulation
Glycyrrhizic acid (in some licorice, cough drops, chewing tobacco)	Mineralocorticoid activity; sodium retention
Herbal supplements: ephedra; 1,3-dimethylamine; synephrine; *N*-methylamine; *Citrus aurantium*; *Caulophyllum thalictroides*	Sympathomimetic
Illicit drugs: amphetamines; cocaine; 3,4-methylenedioxymethamphetamine (ecstasy)	Sympathomimetic
NSAIDs	Sodium retention
Sympathomimetic nonprescription drugs: decongestants (phenylephrine, pseudoephedrine); appetite suppressants; vigilance enhancers	Sympathomimetic

- Identify abnormalities that suggest potential secondary causes from pheochromocytoma, renovascular hypertension, hyperthyroidism, or Cushing syndrome.

Testing

Initial testing is performed to identify common secondary causes, assess for other cardiovascular risk factors, and detect end-organ damage.

- Baseline ECG to assess for left ventricular hypertrophy (end-organ damage) or previous silent myocardial infarction.
- Blood laboratory studies: complete blood count, serum creatinine, estimated glomerular filtration rate (eGFR), serum sodium, potassium, calcium, bicarbonate, fasting glucose, lipid panel, thyroid-stimulating hormone.
- Urinalysis with microscopic examination; in addition, urine albumin-creatinine ratio in patients with diabetes and in those with a high clinical suspicion for underlying CKD, such as a positive family history or presence of other end-organ damage (left ventricular hypertrophy on ECG).
- Echocardiography is not routinely recommended but may be helpful in suspected white coat hypertension in which presence of left ventricular hypertrophy would necessitate treatment with antihypertensive medication, even in the absence of elevated home BP. Echocardiography should also be done to confirm left ventricular hypertrophy suggested by ECG or abnormal cardiac examination.

More extensive diagnostic testing can be pursued if the history, physical examination, or initial testing raises suspicion for secondary causes (**Table 14**).

KEY POINTS

- Initial evaluation of patients with newly diagnosed hypertension includes a complete history, physical examination, and screening laboratory studies to assess for a familial pattern, secondary causes, other cardiovascular risk factors, end-organ damage, and modifiable lifestyle factors.
- Baseline ECG is appropriate for all patients with newly diagnosed hypertension.
- Baseline echocardiography is not routinely recommended, but should be done if examination or ECG suggest cardiac hypertrophy or to evaluate the need for therapy in patients with white coat hypertension.

HVC

TABLE 14. Secondary Causes of Hypertension and Diagnostic Testing

Underlying Cause	Diagnostic Testing
Kidney disease	Serum creatinine; estimated glomerular filtration rate; urinalysis with microscopic examination; urine albumin-creatinine ratio; kidney ultrasonography
Renovascular disease	Renal duplex Doppler ultrasonography; CT or MR angiography; renal artery angiography
Obstructive sleep apnea	Polysomnography
Pheochromocytoma	Plasma fractionated metanephrines; 24-hour urine metanephrines and catecholamines
Hypo- or hyperthyroidism	Thyroid-stimulating hormone; free thyroxine
Primary hyperparathyroidism	Intact parathyroid hormone; serum calcium and phosphorus
Gordon syndrome (pseudohypoaldosteronism type II)	Clinical diagnosis; family history; aldosterone and renin levels; electrolytes
Aortic coarctation	Blood pressure measurements in arms and legs; CT or MR angiography; transthoracic echocardiography
Conditions Associated with Hypokalemia	**Diagnostic Testing**
High aldosterone conditions: Primary hyperaldosteronism: adrenal adenoma (rarely carcinoma or ectopic); bilateral adrenal hyperplasia Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism; >50% normokalemic), type II, or type III Secondary hyperaldosteronism: renal artery stenosis; renin-secreting tumor	Serum sodium and potassium concentrations; plasma aldosterone concentration/plasma renin activity ratio; saline suppression test; CT imaging; adrenal vein sampling; genetic testing
Cushing syndrome	Dexamethasone suppression test; 24-hour urine cortisol excretion; salivary cortisol
Congenital adrenal hyperplasia	Clinical diagnosis
Apparent mineralocorticoid excess	Clinical diagnosis; aldosterone and renin levels; electrolytes
Liddle syndrome	Clinical diagnosis; family history; aldosterone and renin levels; electrolytes

Primary Hypertension

Pathogenesis

Ninety percent of patients with hypertension are identified as having primary (essential) hypertension, in which no secondary underlying etiology can be found. The pathogenesis is still not completely understood, but potential mechanisms include abnormal kidney sodium handling, increased activity of the renin-angiotensin system, and elevated sympathetic tone.

In general, hypertension is a complex polygenic disorder in which many genes or combinations may influence BP. Many genetic variants affect the distal tubular sodium transport and may result in excess sodium retention, leading to hypertension. Genetic polymorphisms involving oxidative stress, mediators of vascular smooth muscle tone, and vasoactive mechanisms have also been implicated. However, associated genetic variants have only small effects, such that the collective effect of all identified BP loci account for only about 3.5% of BP variability. Monogenic forms, in which single gene mutations explain the underlying pathophysiology of hypertension, are less common and include such diseases as glucocorticoid-remediable aldosteronism, Liddle disease, and Gordon syndrome.

Dietary factors have been implicated as contributors to hypertension development. Populations with low sodium intake have lower BP than those with high intake. Habitual high sodium intake along with low potassium intake is a critical factor contributing to the worldwide high prevalence of hypertension. This is especially true for those with salt sensitivity, common in Black patients, older adults, and those with CKD or diabetes, in whom an increase in sodium intake leads to a disproportionate increase in BP.

Positive correlations also exist between BP and physical inactivity, overweight or obesity, excess alcohol intake, hyperuricemia, and insulin resistance.

KEY POINT

- Habitual high sodium intake along with low potassium intake is a critical factor contributing to the worldwide high prevalence of hypertension.

Management

General Approach

Treatment recommendations for specific populations are outlined in respective sections. Importantly, consideration must be given to individual patient characteristics and circumstances to tailor management.

The 2017 ACC/AHA BP guideline provides treatment recommendations, including the following:

- Nonpharmacologic therapy is recommended for those with elevated BP (systolic BP between 120-129 mm Hg and diastolic BP <80 mm Hg) or stage 1 hypertension (systolic BP between 130-139 mm Hg or diastolic BP between 80-89 mm Hg) and a 10-year cardiovascular risk of <10%.
- Nonpharmacologic and drug treatment is recommended for those with BP ≥130/80 mm Hg and clinical cardiovascular disease or a 10-year cardiovascular risk ≥10% to a BP goal of <130/80 mm Hg.
- Nonpharmacologic and drug treatment is recommended for those with no cardiovascular disease and a 10-year cardiovascular risk of <10% for stage 2 hypertension (≥140/90 mm Hg).
- Adults with stage 2 hypertension and an average BP that is 20/10 mm Hg above their BP target should be treated with a combination of two first-line antihypertensive drugs of different classes.
- The target systolic BP goal for noninstitutionalized, ambulatory community-dwelling patients who are ≥65 years of age is <130 mm Hg.
- The target BP for patients with hypertension and diabetes and/or CKD is <130/80 mm Hg.

In 2020, the Department of Veterans Affairs (VA) and Department of Defense (DOD) published guidelines for the diagnosis and management of hypertension in the primary care setting. Although most goals are analogous with those of ACC/AHA, there are some differences:

- The VA/DOD recommend treating patients >60 years of age to a systolic BP goal <150 mm Hg, with the added benefit to lowering BP further for patients whose systolic BP is 130 to 140 mm Hg.
- For patients >60 years of age with type 2 diabetes mellitus, the systolic BP goal is 140 mm Hg, with added benefit from lowering BP to 130 mm Hg.
- The diastolic BP target for all adults >30 years of age is <90 mm Hg.
- The VA/DOD found insufficient evidence to recommend initiating combination therapy over monotherapy with the sequential addition of a second medication.

Lifestyle Modifications

Lifestyle modifications and cardiovascular risk factors should be addressed in all patients with elevated BP or hypertension. Several nonpharmacologic interventions have been shown to have efficacy in reducing BP (**Table 15**). Evidence shows that the most efficacious interventions for BP-lowering effects are weight loss, the Dietary Approaches to Stop Hypertension (DASH) diet, and dietary sodium reduction. Weight reduction is the most efficacious, followed by sodium reduction. Although difficult to achieve, a combination of lifestyle modifications (e.g., DASH combined with a low-sodium diet alone or in combination with weight loss) has BP-lowering effects greater than or equal to those of single-drug therapy in patients with hypertension. The VA/DOD conclude that data are inadequate to recommend weight loss medication or bariatric surgery for the purposes of managing obesity and hypertension. Other effective nonpharmacologic interventions include potassium supplementation (preferably in dietary

TABLE 15. Efficacy of Lifestyle Modifications for Reducing Blood Pressure

Approach	Recommendation	Effect on Systolic Blood Pressure
Reduce weight	BMI <25	5 to 10 mm Hg reduction per 10-kg (22-lb) weight loss
Reduce dietary sodium	1500 to 2400 mg/d	2 to 8 mm Hg reduction
Follow DASH (Dietary Approaches to Stop Hypertension) diet	Fruits; vegetables; low-fat dairy; whole grains; legumes; low saturated fat and sodium; high potassium, magnesium, and calcium	8 to 14 mm Hg reduction
Increase potassium intake	4700 mg/d	Variable reductions
Abstinence of or moderation in alcohol consumption	Men: ≤2 drinks per day; women: ≤1 drink per day	2 to 4 mm Hg reduction
Exercise	30 min/d, most days (not consistently independent of weight loss)	4 to 9 mm Hg reduction
Alternative approaches	Device-guided breathing[a]; yoga; meditation; biofeedback; acupuncture	Variable reductions

[a]Slow breathing exercises, which can be initiated by means of specific devices.

modification), increased physical activity, and abstinence of or moderation in alcohol consumption. Regardless of effects on BP, tobacco cessation should be encouraged given that smoking is a significant risk factor for cardiovascular disease.

Studies evaluating transcendental meditation, yoga, and biofeedback had modest, mixed, or no consistent BP-lowering effects. More data support efficacy of device-guided breathing than acupuncture among the noninvasive procedures and devices that were evaluated.

It is imperative to tailor lifestyle modifications to the individual patient while considering a patient's needs, support systems and resources, and readiness for behavioral change.

KEY POINTS

- The 2017 American College of Cardiology/American Heart Association blood pressure (BP) guideline recommends a BP goal of <130/80 mm Hg in most adult patient populations.
- In addition to lifestyle modification, pharmacologic therapy should be initiated in patients with stage 1 hypertension and clinical cardiovascular disease or a 10-year cardiovascular risk ≥10% and in all patients with stage 2 hypertension.
- Lifestyle modifications (weight loss, diet, dietary sodium reduction) and cardiovascular risk factors should be addressed in all patients with elevated blood pressure and hypertension.

Pharmacologic Therapy

Clinical trials suggest that antihypertensive medication therapy can be associated with up to a 40% reduction in stroke, 25% reduction in myocardial infarction, and 50% reduction in heart failure.

Clinical trials revealed that lowering BP is more important than the agent class used to achieve control. Head-to-head trials of antihypertensive medications revealed comparable effects on cardiovascular outcomes, with one exception: For the prevention of heart failure, initial therapy with a thiazide diuretic was more effective than a calcium channel blocker (CCB) or an ACE inhibitor, and an ACE inhibitor was more effective than a CCB. The primary agents recommended are those that were shown to reduce clinical events and include a thiazide diuretic, CCB, ACE inhibitor, or angiotensin receptor blocker (ARB) for hypertension in the general non-Black population, including those with diabetes. In Black patients, initial antihypertensive therapy should include a thiazide diuretic or a CCB (see Specific Populations, Black Patients).

There are not enough trials comparing β-blockers, central- or peripheral-acting α-blockers, vasodilators, aldosterone receptor antagonists, or loop diuretics to the four drug classes mentioned. Therefore, these drug classes are not recommended as first-line therapy but can be used in specific populations (β-blockers for post–myocardial infarction or heart failure; aldosterone receptor blockers for heart failure; loop diuretics for advanced CKD) or as add-on therapy for resistant hypertension.

Table 16 lists frequently used antihypertensive medications.

Diuretics

Initial antihypertensive treatment may include thiazide diuretics, which act by inhibiting the sodium-chloride-cotransporter in the distal renal tubule. Although hydrochlorothiazide is the most commonly used thiazide, at times chlorthalidone may be preferred because of a prolonged half-life, which allows once-daily dosing. Loop diuretics are preferred in patients with symptomatic heart failure or CKD with an eGFR <30 mL/min/1.73 m^2 (see Kidney Disease, Management).

Suboptimal BP therapy in patients with difficult-to-control hypertension is frequently the result of not including a diuretic, which ensures that extracellular volume expansion is prevented or treated. This is particularly important in

TABLE 16. Frequently Used Antihypertensive Medications

Class/Agent	Common Side Effects/Contraindications
Thiazide diuretics (e.g., hydrochlorothiazide; chlorthalidone)	Hypokalemia; hyponatremia; hyperlipidemia; hyperuricemia; hyperglycemia. Avoid in gout unless patient is on urate-lowering therapy.
ACE inhibitors (e.g., captopril; lisinopril; enalapril; benazepril)	Hyperkalemia; cough. Avoid use with angiotensin receptor blockers or direct renin inhibitors. Contraindicated in pregnancy.
Angiotensin receptor blockers (e.g., candesartan; losartan; valsartan; irbesartan)	Hyperkalemia. Avoid use with ACE inhibitors or direct renin inhibitors. Contraindicated in pregnancy.
Calcium channel blockers	
Dihydropyridines (e.g., amlodipine; felodipine; nifedipine)	Pedal edema; headache; flushing.
Nondihydropyridines (e.g., diltiazem; verapamil)	Constipation. Avoid in HFrEF. Avoid routine use with β-blockers (heart block, bradycardia). Drug interactions (*CYP3A4* major substrate and moderate inhibitor).
β-Blockers (e.g., atenolol; metoprolol tartrate; metoprolol succinate; labetalol)	Fatigue; bronchospasm; sexual dysfunction; hyperglycemia.
Potassium channel openers (vasodilators) (e.g., hydralazine; minoxidil)	Edema. Hydralazine: lupus-like syndrome. Minoxidil: hypertrichosis.
α-Blockers (e.g., prazosin)	Orthostatic hypotension; dizziness.
Central α-agonists (e.g., clonidine, oral or patch)	Fatigue; depression; rebound hypertension.
Potassium-sparing diuretics (e.g., spironolactone; amiloride; eplerenone)	Hyperkalemia. Caution if GFR <45 mL/min/1.73 m^2. Spironolactone: gynecomastia.

GFR = glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction.

sodium-retentive, edematous conditions (heart failure, liver cirrhosis, or CKD). Even in the absence of edematous conditions, persistent intravascular volume expansion without apparent edema can still contribute to hypertension that appears resistant to treatment. In addition, diuretic medication should be prescribed in adequate doses, with dosing frequency tailored appropriately to the diuretic half-life. For example, loop diuretics such as furosemide should be dosed at least twice to three times daily, and higher doses should be used in patients with low GFR.

Potassium-sparing diuretics, such as aldosterone receptor antagonists (spironolactone or eplerenone) or epithelial sodium channel blockers (amiloride), are weaker diuretics. These are often used in patients with liver cirrhosis, heart failure (where evidence suggests reduced mortality), or resistant hypertension. Caution and close monitoring are advised when these medications are prescribed concomitantly with other drug classes that also raise the serum potassium, such as ACE inhibitors, ARBs, or direct renin inhibitors, and in patients with reduced GFR.

Calcium Channel Blockers

There are two classes of CCBs: dihydropyridines (amlodipine, felodipine, nifedipine) and nondihydropyridines (diltiazem, verapamil). No data support the use of one class over the other for hypertension management, although long-acting dihydropyridines are usually chosen. Nondihydropyridines have more pronounced cardiac effects, such as diminished cardiac contractility (negative inotropy) and atrioventricular nodal blockade, and caution should be taken in prescribing these medications concomitantly with β-blockers or in patients with heart failure with severely reduced ejection fraction, sick sinus syndrome, or second- or third-degree atrioventricular block. Additionally, short-acting nifedipine can be associated with increased mortality if used immediately after acute myocardial infarction because of profound hypotension and sympathetic activation. Finally, there may be an increased risk for myopathy if a CCB (especially a nondihydropyridine) is used concomitantly with a high-dose statin.

Renin-Angiotensin System Agents

Renin-angiotensin system (RAS) agents are ACE inhibitors, ARBs, and direct renin inhibitors (such as aliskiren). Clinical trials reported similar efficacy of ACE inhibitors and ARBs on reducing BP, progression of albuminuria and CKD, and risk for cardiovascular events. Therefore, neither class is preferred over the other. There are less outcomes data on the effects of aliskiren, although similar BP-lowering effect is expected.

Dry cough is a side effect of ACE inhibitors but is generally not reported with ARBs. Angioedema, a life-threatening condition, is a complication of both ACE inhibitors and renin inhibitors. Patients with a compelling indication for RAS inhibition who develop angioedema can be treated with an ARB with very careful monitoring, given a low but possible risk for occurrence. RAS agents should not be used in combination, and they are contraindicated in pregnancy.

Combination Therapy

Combination therapy with more than one drug class (separately or as a single-dose pill) may be necessary to control BP.

The 2017 ACC/AHA BP guideline recommends combination therapy with two first-line antihypertensive drugs of different classes for adults with stage 2 hypertension and an average BP of 20/10 mm Hg above their BP target (typically ≥150/90 mm Hg). There are no definitive recommendations for best drug combinations, but some data suggest an ACE inhibitor/CCB combination may be more efficacious than an ACE inhibitor/thiazide diuretic combination. Using a thiazide diuretic/CCB combination is also an option.

Combined use of any RAS drug classes (ACE inhibitors, ARBs, and direct renin inhibitors) is not recommended; several clinical trials (ONTARGET, NEPHRON-D, ALTITUDE) have revealed more adverse events with these combinations (hyperkalemia, hypotension, AKI), without additional cardiovascular or renal benefits.

Assessment of Adherence, Efficacy, and Medication Titration

Adherence and response to treatment should be assessed 4 weeks after treatment initiation or sooner, based on the urgency for BP lowering. Further assessments are necessitated until target is achieved. Three strategies are possible for dose titration:

1. Maximize the first medication dose before adding a second.
2. Add a second medication before reaching the maximum dose of the first.
3. Start with two medication classes separately or as fixed-dose combinations.

There are no randomized trials comparing these strategies; therefore, the strategy should be tailored to the individual patient, dose-related side effects, and adherence. Generally, there is diminishing return in BP lowering if the dose is titrated up from 50% to 100% of maximum. Also, it is unlikely that increasing the dose from 50% to 100% of maximum will result in an additional >5-mm Hg BP reduction; an additional agent may therefore need to be added. Finally, titration to maximum doses may more commonly result in side effects and reduce adherence. Other specific actionable steps to increase adherence include the use of longer-acting antihypertensive drugs that only require once-daily dosing and combination pills to reduce pill burden.

KEY POINTS

- A thiazide diuretic, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker is recommended as initial therapy for hypertension in the general non-Black population, including those with diabetes mellitus.
- Combination therapy with two first-line antihypertensive drugs of different classes is recommended for adults with stage 2 hypertension and an average blood pressure (BP) that is 20/10 mm Hg above their BP target.

White Coat Hypertension

White coat hypertension refers to elevated BP measured in the office, but out-of-office BP averages that are not elevated (see Table 12). Using automated office BP measurements without an observer may lessen the prevalence. In adults with untreated systolic BP >130 mm Hg but <160 mm Hg or diastolic BP >80 mm Hg but <100 mm Hg, it is reasonable to screen for white coat hypertension using either daytime ABPM or home BP monitoring. Before white coat hypertension is diagnosed, the reliability of out-of-office measurements must be confirmed; for example, the patient's home BP monitor should be calibrated against the office sphygmomanometer or, preferably, BP should be measured by ABPM.

The prevalence of white coat hypertension is approximately 15% to 30% among patients with office BP in the hypertensive range. Although these patients may have a slightly higher cardiovascular risk compared with normotensive patients (but a lower risk than in those with masked or sustained hypertension), it is unclear whether antihypertensive drug treatment lowers cardiovascular risk. Lifestyle modification is still recommended in patients with white coat hypertension. However, there is a 1% to 5% per year risk for conversion of white coat hypertension to sustained hypertension. This risk is higher with older age, obesity, or Black race. Annual follow-up with ABPM or home BP measurements should be considered to determine if conversion to sustained hypertension has occurred, requiring the addition of antihypertensive drug therapy. Screening echocardiography may also be considered to screen for left ventricular hypertrophy, the presence of which necessitates treatment with antihypertensives.

KEY POINT

- Lifestyle modifications and careful monitoring should be considered for patients with white coat hypertension because of increased risk for future development of hypertension and slightly higher cardiovascular risk compared with normotensive patients.

Masked Hypertension

Masked hypertension, defined as BP that is normal in the office but elevated in the ambulatory setting (see Table 12), is associated with an increased prevalence of target organ damage and risk for cardiovascular disease, stroke, and mortality compared with normotension. In adults with elevated office BP (120-129/<80 mm Hg) but not meeting the criteria for hypertension or with end-organ damage, such as left ventricular hypertrophy, screening for masked hypertension with daytime ABPM or home BP is reasonable.

The prevalence of masked hypertension varies from 10% to 26% in population-based surveys and from 14% to 30% in

normotensive clinic populations. A 3-month trial of lifestyle modifications should be considered in suspected cases. Antihypertensive treatment should be initiated if daytime ABPM or home BP is still ≥130/80 mm Hg.

KEY POINT

- Masked hypertension is associated with an increased risk for sustained hypertension and cardiovascular disease; after a 3-month trial of lifestyle modifications, antihypertensive medication should be initiated if daytime ambulatory or home blood pressure is still ≥130/80 mm Hg.

Resistant Hypertension

Resistant hypertension is defined as BP that remains above goal despite concurrent use of three antihypertensive agents of different classes, or BP at goal but requiring four or more medications. One of these medications must be a diuretic. A prevalence of 2% to 10% is reported in the general population but can be as high as 40% in patients with CKD. Other risk factors include older age, male sex, Black race, diabetes, and higher BMI.

Before the diagnosis is made, a systematic approach to BP control should include ensuring accuracy of BP readings, confirming adherence to antihypertensive medications, optimizing medication selection and dosing, and addressing potential secondary and reversible causes of hypertension. The importance of out-of-office BP measurements (home or ABPM) as a part of evaluation to rule out white coat hypertension and to confirm resistance is increasingly recognized. Behaviors that could lead to high BP, including excessive sodium consumption, should be reviewed, and use of recreational drugs and prescription or nonprescription medications (such as complementary and alternative medications) that may exacerbate hypertension should be excluded. Adherence to antihypertensive medications, including correct frequency and dosage, should be confirmed, and potential reasons for nonadherence, such as medication side effects, should be addressed.

The cornerstone of management includes a low sodium diet and treatment with an appropriate diuretic with attention to dose and frequency (see Diuretics). Patients should be treated with a combination of medications from different classes: a RAS agent (either an ACE inhibitor, an ARB, or a direct renin inhibitor), a calcium channel blocker, a diuretic, and possibly a β-blocker. Trials support the efficacy of adding a low-dose aldosterone receptor antagonist (spironolactone or eplerenone) for treatment of resistant hypertension. If additional agents are needed for BP control or the patient is intolerant of the aforementioned agents, then vasodilators (hydralazine or minoxidil), α-blockers (doxazosin, prazosin), or central sympathetic agonists (clonidine) can be added.

KEY POINTS

- Resistant hypertension is defined as BP that remains above goal despite the concurrent use of three antihypertensive agents of different classes, or BP at goal but requiring four or more medications; one of the medications must be a diuretic.
- Management of resistant hypertension includes confirming accurate out-of-office BP measurement, addressing behaviors that contribute to high BP, avoiding drugs that exacerbate hypertension, reducing dietary sodium, and ensuring appropriate diuretic dose and frequency.

Secondary Hypertension

In about 10% of adults with hypertension, a specific and remediable cause can be identified. Diagnostic testing for secondary causes of hypertension can be pursued if a high clinical suspicion exists following history, physical examination, and initial laboratory testing (see Table 14). Factors that raise pretest probability for secondary hypertension include hypertension onset at <30 years of age; abrupt-onset or worsening BP if previously well controlled; drug resistance; clinical features indicating a secondary process; presence of target organ damage disproportionate to hypertension duration or severity; diastolic hypertension onset in those ≥65 years of age; and unprovoked or excessive hypokalemia.

Kidney Disease

Pathophysiology and Epidemiology

Hypertension develops in the setting of both AKI and CKD. Underlying parenchymal kidney disease is an important cause of hypertension, and up to 85% of patients with CKD have high BP. Hypertension prevalence increases with GFR decline. Additionally, chronic uncontrolled hypertension is a leading cause of CKD and progression to ESKD. BP elevation in glomerular disease is primarily attributed to fluid overload, as evidenced by suppression of the RAS and increased release of atrial natriuretic peptide. In acute vascular diseases affecting the kidney (vasculitis or scleroderma renal crisis), elevated BP is thought to result from ischemia-induced activation of the RAS. Endothelial injury, increased sympathetic tone, and impaired nitric oxide synthesis are also implicated.

Clinical Manifestations

Underlying kidney disease is suggested by an elevated serum creatinine concentration and/or an abnormal urinalysis or albuminuria. Patients can present with edema, but its absence does not exclude kidney disease as hypertension etiology.

Diagnosis

Initial evaluation of hypertension in all patients includes assessment of serum creatinine and eGFR, urinalysis with microscopic examination to exclude hematuria and/or

proteinuria, and urine albumin-creatinine ratio in those with diabetes or family history of kidney disease. Abnormalities in any of these tests can signify underlying kidney disease. In those with a normal serum creatinine but a high suspicion for certain kidney diseases, such as a positive family history of autosomal dominant polycystic kidney disease, kidney ultrasonography can be undertaken.

Management

The 2017 ACC/AHA BP guideline recommends a BP target of <130/80 mm Hg for patients with hypertension and CKD. An ACE inhibitor or an ARB is a preferred drug for treatment of hypertension for patients with stage G3 CKD or higher or for those with stage G1 or G2 CKD with severe albuminuria (albumin-creatinine ratio ≥300 mg/g).

Kidney function and serum potassium should be reassessed 2 to 3 weeks after initiation of an ACE inhibitor or ARB. An increase in serum creatinine of 25% to 30% is acceptable, but the dose may need to be lowered or medication discontinued if more severe decline in kidney function is observed; in such cases, bilateral renovascular disease should also be considered.

Given that sodium retention and volume overload are major contributory factors in the hypertension of CKD, dietary sodium restriction to <2000 mg/d and addition of a diuretic are both essential for control of BP, especially in advanced CKD. The following factors addressing appropriate dose and dosing interval for diuretics should be considered:

- Higher doses of diuretics are required in patients with CKD due to decreased GFR.
- Thiazide diuretics may be less effective if the eGFR is <30 mL/min/1.73 m^2; although there are no head-to-head trials, it seems preferable to use chlorthalidone instead of hydrochlorothiazide in patients with CKD because of a longer half-life.
- For an eGFR <20 to 30 mL/min/1.73 m^2, a loop diuretic can be used effectively, with a more frequent dosing interval (e.g., furosemide should be dosed at least two to three times daily).
- The combination of a thiazide and a loop diuretic can be used to augment diuresis, with careful monitoring.
- Volume overload refractory to medical management in those with stage G5 CKD (eGFR <15 mL/min/1.73 m^2) may necessitate dialysis.

Renovascular Hypertension

Pathophysiology and Epidemiology

Prevalence of renovascular hypertension is higher in White than in Black populations. Pathogenesis involves renal hypoperfusion as a result of renal artery stenosis, with subsequent release of renin and angiotensin resulting in systemic vasoconstriction, sodium retention, and hypertension. Disease can be unilateral or bilateral. Parenchymal kidney damage with loss of kidney function can occur.

There are two types of renovascular disease: (1) atherosclerotic renovascular disease, which usually occurs in patients >45 years of age, especially in those with diffuse atherosclerosis but can also be isolated to the kidney; and (2) fibromuscular dysplasia, a nonatherosclerotic disorder that usually affects the mid and distal portions of the renal artery and usually occurs in young persons, particularly women.

Clinical Manifestations

Patients with atherosclerotic renovascular disease often have other manifestations of atherosclerosis, including the presence of coronary artery, cerebrovascular, or peripheral vascular disease. Bruits may be auscultated, especially a systolic-diastolic abdominal bruit that lateralizes to one side. Clinical suspicion should be high in patients who present with onset of severe hypertension after age 55 years; recurrent flash pulmonary edema; refractory heart failure; AKI after initiation of an ACE inhibitor/ARB; or AKI after control of BP to target. Asymmetry in kidney sizes of >1.5 cm on imaging or the presence of a unilateral small kidney ≤9 cm also increases the likelihood.

Abrupt onset of hypertension at an age <35 years suggests fibromuscular dysplasia.

Diagnosis

Routine testing for renovascular disease may not change management because recent data suggest that medical therapy may be as beneficial as invasive procedures, especially for those with atherosclerotic renovascular disease. However, in young patients with resistant hypertension and a high clinical suspicion for fibromuscular dysplasia, renal artery imaging may be considered. Plasma renin activity, captopril renal scintigraphy, and selective renal vein renin measurements are no longer recommended given the availability of more sensitive and specific imaging tests.

Renal duplex Doppler ultrasonography is a reasonable imaging modality if performed by experienced sonographers. MR and CT angiography have higher diagnostic utility but are potentially harmful in patients with severe CKD given the risk for contrast-associated nephropathy and gadolinium-induced nephrogenic systemic fibrosis. A stenosis >75% in one or both renal arteries or >50% with post-stenotic dilatation suggests the diagnosis. Renal intra-arterial angiography is the gold standard and can be considered if other noninvasive tests are negative, clinical suspicion is high, and an invasive procedure is contemplated. It is not recommended as a routine test because of adverse risks, such as contrast-associated nephropathy and cholesterol emboli.

Management

Three large randomized trials (STAR, ASTRAL, and CORAL) failed to show that renal artery angioplasty confers additional benefit above optimal medical therapy in patients with atherosclerotic renovascular disease and stable kidney function. Medical therapy includes treatment of underlying

cardiovascular risk factors (such as hypercholesterolemia) and an ACE inhibitor or ARB. Patients who may benefit from percutaneous angioplasty and stenting or surgical intervention include those with the following: a short hypertension duration; atherosclerotic renovascular disease refractory to optimal medical therapy; severe hypertension or recurrent acute flash pulmonary edema; AKI following treatment with an ACE inhibitor or ARB; or progressive impaired kidney function thought to result from bilateral renovascular disease or unilateral stenosis affecting a solitary functioning kidney. Patients with advanced CKD or with proteinuria >1000 mg/24 h are less likely to benefit from revascularization.

Nephrologists or hypertension specialists should be involved in the care of patients with hemodynamically significant renovascular disease, as BP is often difficult to control, the criteria for intervention are complex, and the risk for AKI is increased compared with the typical hypertensive patient population.

In young persons with fibromuscular dysplasia, studies suggest that angioplasty alone may improve BP and even cure hypertension.

Primary Hyperaldosteronism

Primary hyperaldosteronism, in which aldosterone production cannot be suppressed with sodium loading, is the most common cause of secondary hypertension in middle-aged adults and an important cause of resistant hypertension (See MKSAP 19 Endocrinology and Metabolism). A triad of resistant hypertension, metabolic alkalosis, and hypokalemia (including in patients treated with low-dose thiazide diuretics) should raise suspicion (see Table 14). Screening is recommended if any of the following are present: resistant hypertension, hypokalemia (spontaneous or substantial, if diuretic induced), incidentally discovered adrenal mass, family history of early-onset hypertension, moderately severe hypertension (>160/100 mm Hg), or stroke at age <40 years. It is common for patients with primary aldosteronism to have normal potassium; a high index of suspicion is required. Higher cardiovascular morbidity and mortality are noted in patients with primary hyperaldosteronism compared with primary hypertension and similar BP control.

Calculation of plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio is used for screening, with a very high ratio of PAC/PRA suggestive of the diagnosis.

After the diagnosis is confirmed, a dedicated adrenal CT should be performed to determine whether the hyperaldosteronism is caused by diffuse hyperplasia, as seen in two thirds of patients and managed by an aldosterone-receptor antagonist such as spironolactone, versus an aldosterone-producing adenoma amendable to surgical resection.

PAC and PRA are usually suppressed in other disorders with hypokalemia and hypertension, including Cushing syndrome, syndrome of apparent mineralocorticoid excess, familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism), and Liddle syndrome (see Table 14). Renal artery stenosis and renin-secreting tumors generate both high PRA and PAC, with subsequent lowering of the PAC/PRA ratio, to usually <10. See MKSAP 19 Endocrinology and Metabolism for more information.

Pheochromocytomas

Pheochromocytomas are rare catecholamine-secreting neoplasms of the adrenal medulla or sympathetic ganglia that occur in <0.2% of patients with hypertension. Presence of the following characteristics raises clinical suspicion and may prompt testing: resistant hypertension; hypertension onset that is new or at a young age; paroxysmal hypertension; episodic tachycardia, headaches, and sweating; history of familial syndromes; adrenal adenoma found incidentally on imaging with or without hypertension; or pressor response during invasive procedures or anesthesia. Diagnostic tests include plasma fractionated metanephrines and 24-hour urine metanephrines and catecholamines. Positive test results should be followed by imaging to locate the tumor. Definitive treatment is surgical resection. See MKSAP 19 Endocrinology and Metabolism for details.

KEY POINTS

- The 2017 American College of Cardiology/American Heart Association blood pressure (BP) guideline recommends a target BP of <130/80 mm Hg in patients with hypertension and chronic kidney disease.
- An ACE inhibitor or an angiotensin receptor blocker is a preferred drug for treatment of hypertension for patients with stage G3 chronic kidney disease (CKD) or higher and for those with stage G1 or G2 CKD with albumin-creatinine ratio ≥300 mg/g; treatment also includes dietary sodium restriction to <2000 mg/d and addition of a diuretic as needed to control intravascular volume.
- Medical therapy for renovascular disease, including treatment of underlying cardiovascular risk factors and use of an ACE inhibitor or angiotensin receptor blocker, may be as beneficial as invasive procedures.
- Primary hyperaldosteronism is the most common cause of secondary hypertension in middle-aged adults and an important cause of resistant hypertension; the plasma aldosterone concentration/plasma renin activity ratio is used for screening.

Hypertensive Urgency

Hypertensive urgency is defined as severely elevated BP–often a systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg–without obvious signs or symptoms of acute or impending target organ damage or dysfunction. Patients are often asymptomatic or present with a mild headache. The most important aspect of initial management is a focused history and physical examination to exclude the presence of acute end-organ

damage, which would raise concern for hypertensive emergency. Referral to an emergency department may be required for further diagnostic testing.

Management includes the assessment of imminent risk of cardiovascular events from severe hypertension versus risk of adverse sequelae from rapid BP reduction, which include AKI, myocardial infarction, or stroke resulting from decreased organ perfusion and limited time for autoregulation. There are scant data to determine how quickly the BP should be lowered. Generally, systolic BP may be lowered in patients with imminent risk of target organ damage but without acute organ injury (see Hypertensive Emergency) by no more than 25% within the first hour, then to <160/100 mm Hg within the next 2 to 6 hours, then cautiously to target during the following 24 to 48 hours. Choice of antihypertensive medication should be tailored to the specific patient. If there is concern for imminent end-organ damage, faster-acting antihypertensive agents, such as oral clonidine, can be given to lower BP. Several hours of observation in the ambulatory setting may be required to ensure that the patient remains asymptomatic and that BP is decreasing before discharge. In patients in whom hypertensive urgency developed because of medication nonadherence, antihypertensive medications can be resumed slowly in a stepwise fashion, with care not to drop the BP precipitously. Close follow-up is necessary, and further management can include home monitoring of BP.

Hypertensive Emergency

Hypertensive emergency refers to elevated BP significantly above the normal range causing acute organ damage or dysfunction, such as ischemic or hemorrhagic stroke, encephalopathy, AKI, acute myocardial infarction, aortic dissection, or acute heart failure. These effects often occur at BP >180/110 mm Hg, but there is no specific BP threshold above which the syndrome is defined.

Hypertensive emergency should be treated by rapidly lowering the BP, usually using intravenous short-acting agents in the ICU setting (**Table 17** and **Table 18**). The 2017 ACC/AHA BP guideline recommends that for adults with acute organ injury (such as aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma), systolic BP should be reduced to <140 mm Hg during the first hour and to <120 mm Hg in aortic dissection. See MKSAP 19 Neurology for further discussion of the treatment of hypertension associated with ischemic stroke and intracerebral hemorrhage.

KEY POINTS

- Hypertensive urgency is defined as severely elevated blood pressure (BP)–often a systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg–in a patient without obvious signs or symptoms of acute or impending target organ damage or dysfunction.

(Continued)

TABLE 17. Intravenous Antihypertensive Drugs for Treatment of Hypertensive Emergencies

Class	Examples	Comments
Dihydropyridine calcium channel blockers	Nicardipine	Nicardipine: Contraindicated in patients with severe aortic stenosis.
	Clevidipine	Clevidipine: Contraindicated in patients with severe aortic stenosis, soy allergy, egg allergy, hyperlipidemia, lipoid nephrosis, acute pancreatitis.
Vasodilator-nitric oxide dependent	Sodium nitroprusside	Sodium nitroprusside: Intra-arterial blood pressure monitoring recommended. Tachyphylaxis common with prolonged use. Irreversible cyanide toxicity possible with prolonged use.
	Nitroglycerin	Nitroglycerin: Use only for patients with acute coronary syndrome or acute pulmonary edema. Avoid in patients with right ventricular infarction and those taking PDE-5 inhibitors.
Vasodilator-direct	Hydralazine	Not first-line drug because of unpredictable response and long duration of action.
Adrenergic blocker-β_1 selective	Esmolol	Contraindicated with concurrent β-blocker therapy, bradycardia, pulmonary edema, severe HF.
Adrenergic blocker-combined α_1 and nonselective β-blocker	Labetalol	Useful in hyperadrenergic syndromes. Contraindicated in patients with asthma, COPD, heart block. May worsen heart failure.
Adrenergic blocker-nonselective α-blocker	Phentolamine	Useful in patients with pheochromocytoma, cocaine toxicity, amphetamine overdose, clonidine withdrawal.
Dopamine$_1$-agonist	Fenoldopam	Contraindicated in patients with glaucoma or increased intracerebral pressure.
ACE inhibitor	Enalapril	Useful in situations associated with high plasma renin activity (scleroderma renal crisis). Contraindicated in pregnancy, acute MI, bilateral renal artery stenosis.

HF = heart failure; MI = myocardial infarction; PDE = phosphodiesterase.

Data from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e127-e248. [PMID: 29146535] doi:10.1016/j.jacc.2017.11.006

TABLE 18. Intravenous Antihypertensive Drugs for Treatment of Hypertensive Emergencies with Selected Comorbidities

Comorbidity	Preferred Drugs[a]	Comments
Acute aortic dissection	Esmolol, labetalol	Rapid systolic BP lowering to ≤120 mm Hg. β-Blockade should precede vasodilator (such as with nicardipine or nitroprusside) administration.
Acute pulmonary edema	Nitroglycerin, nitroprusside, clevidipine	β-Blockers contraindicated.
Acute coronary syndromes	Esmolol, labetalol, nicardipine, nitroglycerin	Esmolol and nitroglycerin are first-line drugs.
Acute kidney injury	Clevidipine, fenoldopam, nicardipine	–
Eclampsia or preeclampsia	Hydralazine, labetalol, nicardipine	ACE inhibitors, ARBs, renin inhibitors, nitroprusside contraindicated.

ARB = angiotensin receptor blocker; BP = blood pressure.

[a]See Table 17 for specific drug contraindications.

Data from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e127-e248. [PMID: 29146535] doi:10.1016/j.jacc.2017.11.006

KEY POINTS *(continued)*

- For adults with a hypertensive emergency and acute organ injury, systolic blood pressure should be reduced to <140 mm Hg during the first hour and to <120 mm Hg in aortic dissection.

Specific Populations

Women

Hypertension prevalence is lower in women <50 years of age compared with men, but prevalence increases with older age and eventually becomes similar in both sexes. Women, particularly if premenopausal, are at a lower risk than men for hypertension complications, such as coronary artery disease, stroke, and left ventricular hypertrophy. Clinical trials suggest that women derive similar relative benefits from antihypertensive treatment as men, and recommendations for BP targets and agents are the same.

Women of childbearing age who anticipate pregnancy should not be prescribed RAS agents (ACE inhibitors, ARBs, or direct renin inhibitors) because of the risk for urogenital developmental abnormalities; these agents are contraindicated in pregnant women. Instead, transition to methyldopa, nifedipine, and/or labetalol during pregnancy are reasonable choices. See The Kidney in Pregnancy for more information.

Oral contraceptives may be associated with modest increases in BP, which usually resolve with discontinuation; women prescribed these medications should be monitored. Hormone replacement therapy consists of much lower estrogen doses and is not associated with elevated BP.

Patients with Diabetes Mellitus

The 2017 ACC/AHA BP guideline recommends a BP goal of <130/80 mm Hg for patients with diabetes. First-line therapy in non-Black patients with diabetes includes a thiazide diuretic, CCB, ACE inhibitor, or ARB; ACE inhibitors or ARBs are reasonable choices in the presence of albuminuria. In Black patients with diabetes, a thiazide diuretic or CCB is recommended as initial therapy.

The American Diabetes Association (ADA) recommends that patients with diabetes and hypertension with a 10-year atherosclerotic cardiovascular disease (ASCVD) event risk <15% should be treated to a BP goal of 140/90 mm Hg; a lower target of <130/80 mm Hg is appropriate for individuals with existing ASCVD or 10-year ASCVD event risk ≥15%, if this can be achieved safely. The ADA also recommends an ACE inhibitor or ARB, at the maximum tolerated dose indicated for BP treatment, as first-line treatment for hypertension in patients with diabetes and coronary artery disease or a urine albumin-creatinine ratio >300 mg/g; such treatment should also be considered if the urine albumin-creatinine ratio is ≥30 mg/g to 300 mg/g.

Black Patients

Physicians are increasingly aware of the limitations in making management decisions based upon skin color and that labeling patients as Black or not Black may be overly simplistic and inappropriate. Unfortunately, in the absence of more precise genetic markers that help to explain difference in epidemiology and response to therapy among differing patient populations, many experts and guidelines continue to use race-based terminology.

Although hypertension is more prevalent in Black patients and correlates with a higher risk for cardiovascular and kidney outcomes, current recommendations for target BP are similar in Black patients to those in other racial groups. The difference in management is with regard to the agent used. In general, ACE inhibitors are less efficacious in lowering BP in Black patients than are CCBs. Additionally, a landmark trial (ALLHAT) revealed that in Black patients, a thiazide diuretic was more effective in improving cardiovascular outcomes compared with an ACE inhibitor, and there was a higher risk of stroke with use of an ACE inhibitor as initial therapy compared with a CCB. Therefore, in the absence of CKD or heart failure, initial antihypertensive treatment should include a thiazide diuretic or CCB in Black patients. If CKD is present, initial or add-on therapy should include an ACE inhibitor or ARB, especially in those with proteinuria, as

illustrated by the AASK study. Choice of antihypertensive medication in patients with heart failure should be guideline directed.

Older Patients

Prevalence of hypertension increases with age and is as high as 60% to 80% in patients >65 years of age. A wide pulse pressure and isolated systolic hypertension (>160 mm Hg with diastolic <90 mm Hg) are common.

According to the 2017 ACC/AHA BP guideline, the target systolic BP goal for noninstitutionalized, ambulatory community-dwelling patients who are ≥65 years of age is <130 mm Hg. In those with a high burden of comorbidity and limited life expectancy, clinical judgement, patient preference, and an assessment of risk-benefit ratio should be considered.

On the other hand, a 2017 guideline from the American College of Physicians and American Academy of Family Physicians (http://annals.org/aim/article/2598413/pharmacologic-treatment-hypertension-adultsaged-60-years-older-higher-versus) addressed the treatment of hypertension in patients ≥60 years of age, including three recommendations:

- Initiate treatment in patients ≥60 years of age with a systolic BP persistently ≥150 mm Hg to achieve a target systolic BP <150 mm Hg to reduce the risk for mortality, stroke, and cardiac events.
- Consider initiating or intensifying pharmacologic treatment in patients ≥60 years of age with a history of stroke or transient ischemic attack to achieve a target systolic BP <140 mm Hg to reduce the risk for recurrent stroke.
- Consider initiating or intensifying pharmacologic treatment in some patients ≥60 years of age at high cardiovascular risk, based on individualized assessment, to achieve a target systolic BP <140 mm Hg to reduce the risk for stroke or cardiac events.

Non-Black older patients without CKD can be treated with a thiazide diuretic, CCB, or ACE inhibitor or ARB, similar to patients <65 years of age. Antihypertensive medications should be initiated at lower doses with close monitoring of BP and adverse events, given that older individuals are more prone to drug-drug interactions, hyponatremia from thiazide diuretics, and orthostatic hypotension when treated with diuretics, vasodilators, α-blockers, and central-acting drugs (such as clonidine).

KEY POINTS

- Women of childbearing age who anticipate pregnancy should not be prescribed renin-angiotensin system agents because of the risk for urogenital developmental abnormalities.
- In the absence of chronic kidney disease, first-line therapy for hypertension in non-Black patients with diabetes mellitus is similar to treatment of patients without diabetes: a thiazide diuretic, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker.

(Continued)

KEY POINTS *(continued)*

- In the absence of chronic kidney disease or heart failure, initial antihypertensive treatment for Black patients with or without diabetes mellitus includes a thiazide diuretic or calcium channel blocker.
- The 2017 American College of Cardiology/American Heart Association blood pressure (BP) guideline recommends a target systolic BP goal of <130 mm Hg for community-dwelling patients who are ≥65 years of age, whereas the American College of Physicians and American Academy of Family Physicians recommend a target systolic BP goal of <150 mm Hg in patients ≥60 years of age.

Chronic Tubulointerstitial Nephritis

Epidemiology and Pathophysiology

Tubulointerstitial nephritis (TIN) is characterized by damage to the renal tubules and interstitium. TIN can be acute or chronic. Acute interstitial nephritis is commonly due to allergic drug reactions or infection and can cause acute kidney injury within days to weeks. It is characterized by inflammation and edema of the renal interstitium and tubules, which generally improves after the offending drug is discontinued or the underlying disease is treated (see Acute Kidney Injury). Chronic TIN (CTIN) causes a slow decline in kidney function over months and years and is characterized by interstitial scarring, fibrosis, and tubular atrophy. Acute interstitial nephritis can progress to CTIN over time. CTIN can also develop in the setting of chronic primary glomerular disease, vascular diseases, and ischemia secondary to atherosclerosis and hypertension.

Diagnosis and Evaluation

CTIN is often asymptomatic until severe loss of kidney function occurs. Patients frequently present with only an elevated serum creatinine, although they may have symptoms such as polyuria and nocturia due to renal concentrating defects.

A careful history with a review of medications and symptoms suggesting nonpharmacologic triggers should be performed to determine the cause of CTIN (**Table 19** and **Table 20**). A thorough physical examination infrequently provides clues to the diagnosis. Patients may be hypertensive. Urinalysis may be normal or demonstrate pyuria and/or proteinuria <1500 mg/24 h. Nonalbumin proteinuria will require a random (spot) total protein-creatinine ratio determination. See **Table 21** for other laboratory manifestations of CTIN. Kidney ultrasound typically reveals small kidneys if disease is advanced. Kidney biopsy may establish a definitive diagnosis.

TABLE 19. Pharmacologic Causes of Tubulointerstitial Nephritis
Analgesics
Analgesic nephropathy (e.g., aspirin, caffeine, acetaminophen, NSAIDs [including COX-2 inhibitors]), or NSAID combinations)
Antibiotics
Penicillins (e.g., amoxicillin, methicillin, oxacillin)
Cephalosporins (e.g., cefazolin, cephalexin, cefoxitin)
Fluoroquinolones (e.g., ciprofloxacin, levofloxacin)
Sulfonamides (e.g., trimethoprim-sulfamethoxazole)
Macrolides (e.g., azithromycin, clarithromycin)
Rifampin
Calcineurin Inhibitors
Cyclosporine
Tacrolimus
Antineoplastics
Immune checkpoint inhibitors (e.g., atezolizumab, ipilimumab)
Tyrosine kinase inhibitors (e.g., sorafenib, sunitinib)
Ifosfamide
Pemetrexed
Lenalidomide
Vemurafenib
Nitrosoureas (e.g., streptozotocin, semustine)
Gastrointestinal Therapeutics
Proton pump inhibitors (e.g., omeprazole, pantoprazole)
H_2 blockers (e.g., ranitidine)
5-Aminosalicylates (e.g., mesalazine, sulfasalazine)
Sodium phosphate (can cause phosphate nephropathy)
Drugs of Abuse
Synthetic cannabinoids
Anabolic androgenic steroids
Toluene
Cocaine
Other
Antiretrovirals (e.g., abacavir, indinavir, tenofovir)
Allopurinol
Diuretics (e.g., thiazide, loop, potassium sparing)
Lithium
Antiepileptic drugs (e.g., carbamazepine, phenytoin, phenobarbital)
Antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers, calcium channel blockers)
Prolonged exposure to any medication that can cause acute interstitial nephritis

TABLE 20. Nonpharmacologic Causes of Chronic Tubulointerstitial Nephritis
Immunologic Diseases
Sarcoidosis
Sjögren syndrome
Systemic lupus erythematosus
IgG4-related disease
Tubulointerstitial nephritis with uveitis (TINU)
Vasculitis
Toxic Causes
Aristolochic acid (Balkan) nephropathy (urologic evaluation is indicated due to increased risk for transitional cell [urothelial] carcinoma)
Heavy metal nephropathy (e.g., lead, cadmium, mercury, arsenic, bismuth, chromium, copper, gold, iron, uranium)
Chronic interstitial nephritis in agricultural communities
Hereditary Tubulointerstitial Nephritis
Medullary cystic kidney disease
Mitochondrial disorders
Nephronophthisis
Infection-Related Causes
Viruses (notably, BK polyoma virus after kidney transplantation, HIV)
Fungal infections
Parasitic infections
Spirochetes
Chronic pyelonephritis
Bacterial infections (e.g., brucellosis, tuberculosis)
Malignancy-Related Causes
Leukemia
Lymphoma
Malignancy-associated monoclonal gammopathies (e.g., multiple myeloma, plasmacytoma)
Metabolic Disorders
Oxalate nephropathy
Uric acid nephropathy
Nephrocalcinosis
Hypokalemic nephropathy
Urinary Tract Obstruction
Obstructive uropathy
Nephrolithiasis
Reflux disease

TABLE 21. Laboratory Manifestations of Chronic Tubulointerstitial Nephritis

Abnormality[a]	Causes
Decline in GFR	Obstruction of tubules; damage to microvasculature; interstitial fibrosis and sclerosis of glomeruli
Proximal tubular damage (Fanconi syndrome)	Incomplete absorption and kidney wasting of glucose, phosphate, uric acid, bicarbonate, and amino acids
Normal anion gap metabolic acidosis	Proximal and distal RTA; decreased ammonia production
Polyuria and isosthenuria	Decreased concentrating and diluting ability
Proteinuria	Decreased tubular protein reabsorption (usually <1500 mg/24 h)
Hyperkalemia	Defect in potassium secretion (type 4 [hyperkalemic] distal RTA)
Hypokalemia	Defect in potassium reabsorption (type 1 [hypokalemic] distal RTA)
Anemia	Injury to erythropoietin-producing cells in the kidney

GFR = glomerular filtration rate; RTA = renal tubular acidosis.

[a]The degree of these abnormalities depends on the extent and location of injury.

KEY POINTS

- Chronic tubulointerstitial nephritis is characterized by interstitial scarring, fibrosis, and tubular atrophy and results in a slow decline in kidney function over months and years.
- Features of chronic tubulointerstitial nephritis include polyuria and nocturia due to renal concentrating defects; hypertension; and a urinalysis that is normal or demonstrates pyuria and/or proteinuria <1500 mg/24 h.
- Some clinical features of chronic tubulointerstitial nephritis may reflect tubular dysfunction, including glucosuria and other features of Fanconi syndrome, normal anion gap metabolic acidosis, hypokalemia, or hyperkalemia.

Causes

See Table 19 and Table 20 for the pharmacologic and nonpharmacologic causes of TIN.

Immunologic Diseases

Sjögren Syndrome

Kidney involvement in Sjögren syndrome may include interstitial nephritis, distal (type 1) renal tubular acidosis (RTA), and glomerulonephritis. Nephrolithiasis, nephrocalcinosis, and progressive kidney disease may also occur.

Sarcoidosis

Kidney involvement in sarcoidosis is not uncommon and can manifest as nephrocalcinosis from hypercalcemia and hypercalciuria, obstructive uropathy, and TIN with granuloma formation. Kidney recovery is often incomplete.

Systemic Lupus Erythematosus

TIN may occur in systemic lupus erythematosus and is often associated with concurrent glomerular disease, but can also be the only manifestation of lupus nephritis. The severity of TIN is a useful predictor of progressive kidney disease.

IgG4-Related Disease

TIN is the most common renal manifestation of systemic IgG4-related disease and is characterized by abundant IgG4-positive plasma cell interstitial infiltrates. Other features may include hypocomplementemia, peripheral eosinophilia, and renal masses. See MKSAP 19 Rheumatology for more information.

Infections

Certain infections are associated with acute interstitial nephritis and can contribute to CTIN. Etiologies include bacterial (such as brucellosis and tuberculosis), viral, fungal, and parasitic infections.

In immunosuppressed patients with kidney transplants, BK polyoma virus causes an interstitial nephritis that is difficult to distinguish by biopsy from acute cellular rejection. Urine and serum BK polyoma virus polymerase chain reaction titers and a specific BK stain (SV40) help determine etiology. The most effective intervention is reduction of immunosuppressive therapy.

Chronic pyelonephritis resulting from chronic infections or vesicoureteral reflux may cause CTIN. Patients may present with fever, chills, dysuria, flank or back pain, and hypertension. Persistent chronic pyelonephritis can progress to localized xanthogranulomatous pyelonephritis, which is characterized by a destructive mass that invades the renal parenchyma.

Malignancy

Lymphoma and acute leukemia can infiltrate the kidney, causing TIN. Presenting features include proteinuria, sterile pyuria, and enlarged kidneys. Plasma cell dyscrasias such as multiple myeloma can cause TIN in the form of myeloma cast nephropathy, Fanconi syndrome, or interstitial light chain deposition.

Medications

Medication-induced acute interstitial nephritis (Table 19) may evolve to CTIN due to protracted exposure to an offending agent. The most common associated drug classes include antibiotics, NSAIDs, and proton pump inhibitors.

Analgesics

Analgesic nephropathy was first described in patients taking combinations of phenacetin (banned since 1983) with aspirin, caffeine, acetaminophen, or NSAIDs. It can also occur with the individual drugs. When severe, analgesic nephropathy is associated with renal papillary necrosis, manifesting as gross

hematuria, flank pain, and, occasionally, obstruction and infection. Affected individuals typically have a history of heavy analgesic use.

Calcineurin Inhibitors

The calcineurin inhibitors cyclosporine and tacrolimus can cause CTIN. Longer durations of exposure increase risk for CTIN. Associated thrombotic microangiopathy is uncommon but may contribute to acute or chronic kidney injury.

Lithium

Lithium exposure can cause distal tubular dysfunction (type 1 hypokalemic distal RTA), nephrogenic diabetes insipidus, and CTIN. CTIN occurs in up to 15% to 20% of long-term lithium users. Risk factors for CTIN include advanced age, cumulative dose, and repeated episodes of lithium toxicity with high serum levels. Kidney dysfunction can progress to end-stage kidney disease even after discontinuation of lithium.

Antineoplastic Agents

Multiple chemotherapy agents can cause TIN. Immune checkpoint inhibitors and tyrosine kinase inhibitors are the main classes implicated. Other associated agents with TIN include ifosfamide, pemetrexed, lenalidomide, vemurafenib, and nitrosoureas (particularly streptozotocin and semustine).

Drugs of Abuse

Drugs of abuse such as synthetic cannabinoids, anabolic androgenic steroids, toluene, and cocaine are associated with acute interstitial nephritis. The incidence of CTIN associated with repeated exposure is unknown.

Lead

Lead can result in tubular dysfunction and CTIN. Occupational exposure to lead occurs from welding, smelting, the battery industry, and mining. Toxicity may also develop after months to years of exposure to lead in water, soil, paint, or food products. Gout is common. The clinical diagnosis of lead nephropathy is based on history of exposure, evidence of kidney dysfunction, and blood lead levels. Levels may be normal if lead exposure has abated.

Chronic Interstitial Nephritis in Agricultural Communities

Chronic interstitial nephritis in agricultural communities (CINAC) is an emerging public health problem in many Central American and Asian countries. CINAC is observed most commonly in young- to middle-age male agricultural workers and often progresses to end-stage kidney disease. The precise etiology is uncertain, but it is postulated that there is an association with frequent dehydration, pesticide exposure, and other environmental contaminants.

Aristolochic Acid Nephropathy

Aristolochic acid nephropathy (Balkan nephropathy) is a cause of CTIN first described in Southeast Europe and later identified in consumers of certain Chinese herbs. It is caused by ingestion of a toxin from the *Aristolochia clematitis* plant. Aristolochic acid nephropathy is associated with progression to end-stage kidney disease as well as urothelial cancers. Cystoscopy with retrograde pyelography should be performed in patients with aristolochic acid nephropathy and nonglomerular hematuria.

Obstruction

Obstructive uropathy from prostate disease, malignancy, nephrolithiasis, pelvic radiation, medications such as methysergide, and retroperitoneal fibrosis can cause CTIN and progressive kidney dysfunction. RTA, hyperkalemia, and mild proteinuria are common.

KEY POINTS

- Causes of chronic tubulointerstitial nephritis include various immunologic diseases, infections, malignancy, medications, drugs of abuse, lead, and obstructive uropathy.
- More recently recognized risk factors for chronic tubulointerstitial nephritis include chronic interstitial nephritis in agricultural communities, affecting young- to middle-age male agricultural workers, as well as aristolochic acid nephropathy from the ingestion of a Chinese herb toxin.

Management

Management of acute and chronic TIN involves treating the underlying cause by discontinuing medications, drugs of abuse, or toxin exposure; administering immunosuppressive therapy (often glucocorticoids) for immunologic or drug-related allergic causes; treating infection or malignancy; and relieving obstruction. Treatment of lead nephropathy consists of ethylenediaminetetraacetic acid chelation therapy or oral succimer. In patients with CTIN and progressive kidney disease, management includes control of blood pressure and treatment of proteinuria and metabolic abnormalities (see Chronic Kidney Disease).

Glomerular Diseases

Epidemiology and Pathophysiology

Glomerular diseases are the third leading cause of end-stage kidney disease (ESKD) in the United States, accounting for approximately 10,000 incident cases of ESKD per year and trailing only diabetes mellitus and hypertension. The term *glomerular disease* encompasses a wide array of conditions

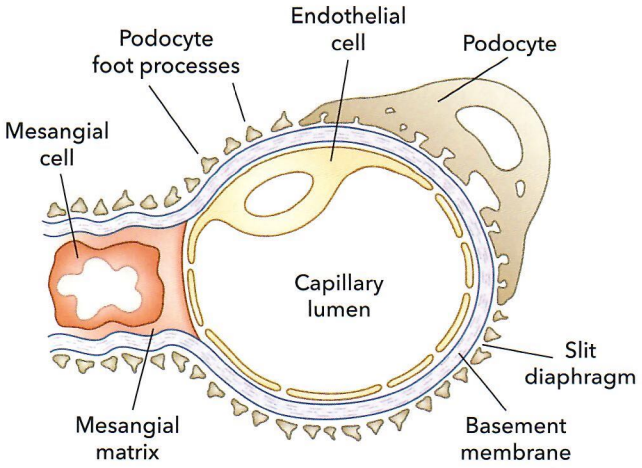


FIGURE 13. The podocyte, a visceral epithelial cell, sits on the outside surface of the glomerular basement membrane.

with etiologies that span autoimmune disease, malignancy-associated conditions, sequelae of infection, genetic mutations, and medication toxicities. These diseases are classified as either primary (idiopathic), in which the glomerular injury is an intrinsic process generally limited to the kidney, or secondary, in which the glomerular lesion is the result of a systemic disease with kidney involvement as one of many possible manifestations.

The normal, noninflamed glomerulus forms a tight barrier, largely due to the slit diaphragms that connect podocyte (visceral epithelial cell) foot processes on the outside surface of the glomerular basement membrane (**Figure 13**). When healthy, this filtration barrier prevents passage of blood and protein into the urinary filtrate. Glomerular diseases involve injury of the glomerular filter with subsequent passage of protein (proteinuria) and, in the setting of glomerulonephritis, blood (hematuria) into the urine. These urinary abnormalities are the earliest manifestations of a glomerular lesion. When left untreated, these injuries may result in scarring of the glomerular filters (glomerulosclerosis) with subsequent decline in kidney function.

Most etiologies of glomerular disease are diagnosed via kidney biopsy. No formal guidelines exist for the indications to perform a kidney biopsy in any age group. The decision to pursue a kidney biopsy when glomerular disease is suspected should be individualized for each patient, but, in general, a kidney biopsy appears justified for patients with an otherwise unexplained combination of the following four findings: hematuria; proteinuria >1000 mg/24 h; reduced kidney function (glomerular filtration rate <60 mL/min/1.73 m^2); and/or positive serologies for systemic diseases with known potential for kidney involvement (for example, hepatitis B or C virus infection, systemic lupus erythematosus, and ANCA seropositivity). The risks of kidney biopsy, mainly bleeding, should always be weighed against the benefits of establishing a more precise diagnosis and treatment plan.

Clinical Manifestations of Glomerular Disease

The two main categories of glomerular disease are the nephrotic and nephritic syndromes, each of which has a distinct clinical presentation.

The Nephrotic Syndrome

Clinical manifestations of the nephrotic syndrome stem from ongoing loss of protein, principally albumin, into the urine. This urinary loss of albumin causes hypoalbuminemia; in response, the liver increases its production of several proteins, including cholesterols, leading to hyperlipidemia. The resulting hallmark features of the nephrotic syndrome include the following:

- Urine protein excretion >3500 mg/24 h or a urine protein-creatinine ratio >3500 mg/g (nephrotic-range proteinuria)
- Hypoalbuminemia (usually <3.0 g/dL [30 g/L])
- Hypercholesterolemia
- Edema

Edema is typically most severe in the lower extremities. Many patients report periorbital edema upon awakening. Severe fluid retention can lead to pulmonary edema, pulmonary effusions, and anasarca. Despite avid salt and water retention, hypertension occurs only in a minority of patients.

Two explanations have been proposed for the edema seen in the nephrotic syndrome. The "underfill hypothesis" argues that low serum albumin concentrations lead to a reduction in intravascular oncotic pressure and a resultant shift of plasma from the capillary lumen to the interstitium. The consequent intravascular depletion activates the renin-angiotensin system (RAS), which promotes salt and water retention throughout the nephron, exacerbating the edema. In contrast, the "overfill hypothesis" argues that sodium is primarily retained at the collecting duct, triggered by the abnormally filtered proteins themselves. Both hypotheses may be correct, and both provide a rationale for edema management in patients with the nephrotic syndrome. First, resolution of edema is only attainable long term by remission of proteinuria; lending support to the overfill hypothesis, edema will often subside when proteinuria has fallen but before albumin has returned to normal range. Second, diuretics and dietary sodium restriction are crucial to control the symptoms of edema.

The nephrotic syndrome is a hypercoagulable state. In addition to albuminuria, patients with the nephrotic syndrome excrete a number of low-molecular-weight anticoagulants (for example, antithrombin III, protein S) and fibrinolytics (for example, plasminogen). Hepatic overproduction of proteins, as an intrinsic response to hypoalbuminemia, leads not only to hyperlipidemia but also to increased levels of procoagulants (for example, factor V, factor VIII, fibrinogen). As a result, patients with the nephrotic syndrome are at increased risk for lower extremity, pulmonary, and renal vein thrombosis.

Clots are most often seen in patients with membranous nephropathy, but any patient with nephrotic-range proteinuria and significant hypoalbuminemia (usually <2.5 g/dL [25 g/L]) should be considered at risk, especially early in the course of the disease. Patients with the nephrotic syndrome are also at higher risk for arterial thrombosis than the general population.

Albuminuria should be treated with RAS-blocking drugs to control blood pressure and reduce proteinuria. Hyperlipidemia should be treated with statin therapy. This combination of RAS-blocking drugs, statins, and diuretics is generally considered conservative therapy for most forms of glomerular disease. A general strategy for edema management in a patient with newly diagnosed nephrotic syndrome is to start with a loop diuretic and a goal weight loss of 1 to 2 kg (2.2-4.4 lb) per week. In severe cases of edema when loop diuretics have been maximally up-titrated and weight loss/edema control are insufficient, it is often necessary to add a second diuretic (a thiazide diuretic and/or potassium-sparing diuretic) that works distal to the loop of Henle. In patients taking high doses of loop diuretics, increased delivery of salt and water to the distal portions of the nephron can lead to hypertrophy of these segments and overabsorption of sodium, undermining the effects of the loop diuretic.

The Nephritic Syndrome

The nephritic syndrome, also termed *glomerulonephritis*, can present as a number of clinical variants. Common features are hematuria (microscopic or macroscopic) and proteinuria with the more severe variants typically including hypertension, edema, and kidney dysfunction (elevated serum creatinine). The glomerular hematuria seen in the nephritic syndrome can be distinguished from other causes of urinary tract bleeding by the presence of either dysmorphic erythrocytes (resulting from passage through a damaged glomerular basement membrane) or erythrocyte casts on urine microscopy (see Clinical Evaluation of Kidney Function).

The mildest forms of the nephritic syndrome are asymptomatic, with microscopic hematuria with or without proteinuria often discovered on routine laboratory assessment. Recurrent gross hematuria, in which the hematuria occurs several days after an upper respiratory infection or physical exertion, is a classic presentation of IgA nephropathy, particularly in younger patients. This nephritic presentation also usually follows a benign clinical course without associated chronic kidney disease.

On the other hand, the term *acute glomerulonephritis* is used to denote the more classical nephritic syndrome presentation, with variable degrees of kidney dysfunction, hypertension, edema, proteinuria, and hematuria. The most severe form of the nephritic syndrome is termed *rapidly progressive glomerulonephritis*, in which patients experience a rapid decline of kidney function over days or weeks that will progress to ESKD if untreated.

KEY POINTS

- The hallmark features of the nephrotic syndrome include a urine protein excretion >3500 mg/24 h or a urine protein-creatinine ratio >3500 mg/g, hypoalbuminemia, hypercholesterolemia, and edema.
- Common features of the nephritic syndrome are hematuria (with dysmorphic erythrocytes or erythrocyte casts) and proteinuria; hypertension, edema, and kidney dysfunction may also occur.

Conditions Associated with the Nephrotic Syndrome

Diabetic Kidney Disease

Epidemiology and Pathophysiology

Diabetes mellitus is the leading cause of chronic kidney disease (CKD) and ESKD worldwide. In the United States, diabetes accounts for >50,000 new cases of ESKD requiring dialysis each year. Diabetic kidney disease (DKD), defined as clinical evidence of kidney injury in response to chronic, long-standing hyperglycemia, is detected in approximately 10% of patients with type 1 diabetes and 35% to 50% of patients with type 2 diabetes.

Advanced glycation end products are believed to be the primary mediator of injury in DKD, activating signaling cascades that promote endothelial injury and mesangial cell synthesis of profibrogenic cytokines.

Clinical Manifestations

DKD manifests initially as mildly increased albuminuria. Over time, in some patients, progressive proteinuria is followed by a decline in glomerular filtration rate, with progression to later stages of CKD and ESKD.

DKD is often accompanied by extrarenal microvascular complications of diabetes, including retinopathy and peripheral neuropathy as well as macrovascular complications, such as peripheral vascular disease, coronary artery disease, and stroke.

Diagnosis

The American Diabetes Association recommends yearly assessment of albuminuria in patients with type 2 diabetes, and assessment after 5 years of disease in patients with type 1 diabetes. The diagnosis of DKD is usually made clinically in the presence of hallmark features: proteinuric CKD in a patient with long-standing diabetes and evidence of other (microvascular and/or macrovascular) complications of disease. If the clinical presentation is not entirely consistent with DKD, a kidney biopsy is performed. The biopsy finding of nodular mesangial sclerosis with glomerular and tubular basement thickening, in the absence of immune deposits, is the classic description of DKD.

Treatment and Prognosis

The cornerstone of treatment of DKD involves glycemic control and blood pressure control. Blockade of the RAS with an

ACE inhibitor or angiotensin receptor blocker (ARB) is recommended, typically to the maximal tolerated dose, because these agents both reduce blood pressure and levels of proteinuria, which, along with glycemic control, are the most important modifiable risk factors for progression of DKD to ESKD. Combined use of any two of the three RAS drug classes (ACE inhibitors, ARBs, and direct renin inhibitors) is not recommended given the results of several clinical trials that revealed more adverse events with these combinations (hyperkalemia, hypotension, acute kidney injury [AKI]) without additional cardiovascular or renal benefits. Combining ACE inhibitors or ARBs with mineralocorticoid receptor blockers (spironolactone or eplerenone) has been shown in small studies to be a safe and effective antiproteinuric strategy in DKD, but the risk for hyperkalemia should be considered and monitored appropriately. For patients with type 2 diabetes and CKD, the American Diabetes Association recommends that physicians consider use of a sodium–glucose cotransporter 2 inhibitor when the estimated glomerular filtration rate is >30 mL/min/1.73 m^2 with a urine albumin-creatinine ratio >30 mg/g. The recommendation is more strongly advised in patients with a higher-grade albuminuria (urine albumin-creatinine ratio >300 mg/g), in which the sodium–glucose cotransporter 2 inhibitor will reduce progression of kidney disease and/or cardiovascular events. In patients with CKD who have additional cardiovascular risk factors, a glucagon-like peptide 1 receptor agonist will also reduce the risk for CKD progression, cardiovascular events, or both.

The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) blood pressure guideline recommends a blood pressure target of <130/80 mm Hg for patients with hypertension and diabetes and/or CKD. The American Diabetes Association recommends that most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mm Hg and a diastolic blood pressure goal of <90 mm Hg; lower systolic and diastolic blood pressure targets, such as 130/80 mm Hg, may be appropriate for individuals at high risk for cardiovascular disease if they can be achieved safely.

KEY POINTS

- The American Diabetes Association recommends yearly assessment of albuminuria in patients with type 2 diabetes mellitus, and assessment after 5 years of disease in patients with type 1 diabetes mellitus.
- The cornerstone of treatment of involves glycemic control and blood pressure control with an ACE inhibitor or angiotensin receptor blocker, titrated to maximal tolerated dose.
- HVC In the treatment of diabetic kidney disease, combining any two renin-angiotensin system drug classes (ACE inhibitors, angiotensin receptor blockers, or direct renin inhibitors) is not recommended, as side effects are increased and there is no additional clinical benefit.

(Continued)

KEY POINTS *(continued)*

- For patients with type 2 diabetes mellitus and chronic kidney disease, the American Diabetes Association recommends that physicians consider therapy with a sodium–glucose cotransporter 2 inhibitor or a glucagon-like peptide 1 receptor agonist to delay progression of kidney disease and decrease cardiac mortality.

Focal Segmental Glomerulosclerosis

Epidemiology and Pathophysiology

Following DKD, focal segmental glomerulosclerosis (FSGS) is the most common form of primary nephrotic syndrome in Black patients and, in certain parts of the world, has replaced membranous nephropathy as the leading cause of the nephrotic syndrome in White patients.

FSGS stems from abnormalities in the podocyte. Podocyte detachment and death lead to the segmental sclerosis that is the hallmark histopathology of FSGS. The podocyte injury in FSGS, in turn, can stem from immunologic, genetic, and/or glomerular hyperfiltration causes and may be primary or secondary, which is associated with a more systemic process. Immunologic injury is considered the main pathogenic mechanism behind primary forms of FSGS, with leukocytes producing a soluble circulating factor that directly targets podocytes. This mechanism is supported by cases of FSGS recurring almost immediately after kidney transplantation and responding briskly to plasmapheresis, although definitive identification of such a circulating factor has yet to occur. Identified genetic causes of FSGS are chiefly mutations in podocyte-specific proteins (for example, nephrin, podocin, formin). These mutations are more commonly found in infants, young (<25 years of age) patients who do not respond to glucocorticoid therapy, and patients with a family history of ESKD. Individuals of African ancestry carry approximately a five times higher risk for FSGS than those of European descent (see Genetic Disorders and Kidney Disease). Hyperfiltration, the third mechanism and major form of secondary FSGS, is seen classically in patients with obesity but also can manifest in patients with a history of premature birth or solitary kidney. Finally, drug-induced FSGS can occur as a rare complication of some commonly used treatments, including lithium, interferon, and pamidronate.

Clinical Manifestations

All patients with FSGS have proteinuria, ranging from severe with other features of classic nephrotic syndrome, to more modest with otherwise asymptomatic proteinuria. Any form of FSGS can present with reduced glomerular filtration rate, particularly when diagnosed late in the disease course.

Diagnosis

FSGS is diagnosed by kidney biopsy. On light microscopy, glomerulosclerosis (scarring of glomeruli) is seen in a focal (<50%) and segmental (affecting a portion but not the entirety

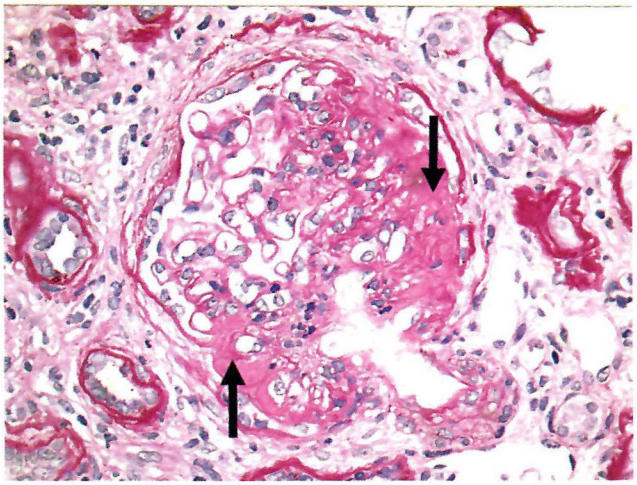


FIGURE 14. Light microscopy in focal segmental glomerulosclerosis shows scarring (*arrows*) in some, but not all, glomeruli in a segmental distribution, as demonstrated by this glomerulus.

Courtesy of Glen Markowitz, MD.

of individual glomeruli) distribution (**Figure 14**). Histologic variants of FSGS include classic FSGS, perihilar variant, glomerular tip lesion variant, cellular variant, and collapsing variant. The collapsing variant, associated with HIV infection but also seen in individuals not infected with HIV, is often resistant to treatment and therefore carries the worst long-term prognosis, whereas the tip lesion usually responds to glucocorticoids and is unlikely to progress to ESKD.

Treatment and Prognosis

For all patients with FSGS, conservative therapy includes RAS-blocking drugs to control proteinuria, statin therapy, and edema management. Such conservative therapy measures suffice for patients who have FSGS with subnephrotic proteinuria.

When nephrotic-range proteinuria is present and if a primary form of FSGS is suspected, high-dose glucocorticoids remain the mainstay of initial therapy. Other immunosuppressants, including calcineurin inhibitors, mycophenolate mofetil, alkylating agents, and rituximab, have been reported to provide some benefit as second-line agents for patients who either do not respond to glucocorticoids or whose proteinuria relapses when glucocorticoids are tapered off.

Approximately 50% of patients with FSGS progress to ESKD within 10 years of diagnosis; this poor prognosis is rooted in low rates of treatment response.

KEY POINT

- Initial treatment of primary focal segmental glomerulosclerosis is high-dose glucocorticoids.

Membranous Nephropathy

Epidemiology and Pathophysiology

Membranous nephropathy (also known as membranous glomerulopathy) is a leading cause of the nephrotic syndrome in White adults. Epidemiology has remained constant over the past several decades, with a peak incidence between 30 and 50 years of age. Approximately 75% of cases are considered primary; the remaining 25% are considered secondary to systemic diseases such as systemic lupus erythematosus, hepatitis B virus infection, medications (for example, penicillamine), and solid tumors.

In the past decade, target antigens and their associated autoantibodies responsible for the development of primary membranous nephropathy cases have been identified. The M-type phospholipase A2 receptor (PLA2R) is the specific podocyte antigen responsible for eliciting immune complex formation with circulating autoantibodies in most primary cases. Anti-PLA2R antibodies are detected in approximately 75% of primary cases and are rarely found in secondary forms. Additional alternative podocyte autoantigens have been reported in patients with primary membranous nephropathy, potentially filling in the missing gaps in PLA2R antibody-negative disease. Membranous nephropathy occurs when circulating antibodies permeate the glomerular basement membrane and form immune complexes with epitopes on podocyte membranes.

Clinical Manifestations

Patients with membranous nephropathy typically describe slowly progressive edema, and laboratory testing reveals proteinuria, hypoalbuminemia, and hyperlipidemia, most often with preserved kidney function. Patients are particularly prone to thrombotic complications. These clots include lower extremity, pulmonary, and renal vein thromboses; they can occur in up to 25% of patients and are most likely to occur within the first 2 years of diagnosis. The risk of clotting increases when serum albumin is <2.8 g/dL (28 g/L) and is highest when serum albumin is <2.2 g/dL (22 g/L).

Diagnosis

The diagnosis of membranous nephropathy is traditionally made by kidney biopsy, although testing for anti-PLA2R antibodies has introduced the possibility of diagnosing the disease noninvasively. The presence of anti-PLA2R antibodies may eliminate the need for kidney biopsy in patients with preserved kidney function and no evidence of secondary causes as well as in patients with a clear contraindication to kidney biopsy (for example, patients on anticoagulants that cannot be discontinued).

The hallmark biopsy finding is the presence of subepithelial immune deposits that alter the glomerular capillary wall, classically accompanied by intervening "spikes" of glomerular basement membrane extending between the immune deposits in more advanced cases. The biopsy can be stained for the PLA2R antigen, which typically yields a higher sensitivity (>80%) than antibody testing in the serum and helps confirm primary rather than secondary disease. Such a distinction is crucial because secondary forms are expected to remit if the underlying systemic disease responsible for the lesion is successfully treated. Notably, in patients with membranous

nephropathy aged 65 years and older, malignancies have been detected in up to 25% within 1 year of their biopsy diagnosis. Therefore, age-, sex-, and risk factor–appropriate cancer screening is recommended for all patients at the time of their diagnosis, even those with PLA2R positivity.

Treatment and Prognosis

Patients with newly diagnosed primary forms of membranous nephropathy are usually observed for 6 to 12 months on conservative therapy (RAS blockade, statin therapy, and edema management) before initiating a course of immunosuppression for patients with persistent nephrotic-range proteinuria. The observation period allows patients a chance to achieve spontaneous remission, which occurs in approximately 30% within 1 to 2 years of diagnosis. Three first-line immunosuppressive regimens are available for patients who remain nephrotic: (1) a combination of glucocorticoids and alkylating agents, which achieves remission in approximately 75% to 80% of patients within 12 months, (2) calcineurin inhibitors (cyclosporine or tacrolimus), which have reported remission rates of 70% to 75% in the first year of therapy but for which relapse rates are higher in patients treated with calcineurin inhibitors than alkylating agents, or (3) rituximab, which was noninferior compared with cyclosporine in inducing remission of proteinuria and proved superior in maintaining that remission; adverse events were lower in the group treated with rituximab compared with cyclosporine. Treatment of secondary forms of membranous nephropathy should be aimed at the underlying systemic disease or etiology.

Progression to ESKD depends on remission of proteinuria: The 10-year incidence of ESKD in patients who undergo complete or partial remission of proteinuria ranges from 0 to 10%, compared with a >50% incidence of ESKD in patients who maintain nephrotic-range proteinuria.

KEY POINT

HVC
- Primary membranous nephropathy is typically treated with conservative therapy before initiating immunosuppression for patients with persistent nephrotic-range proteinuria to allow for spontaneous remission, which occurs in approximately 30% of patients.

Minimal Change Glomerulopathy

Epidemiology and Pathophysiology

Minimal change glomerulopathy (MCG; also known as minimal change disease) is the most common cause of the nephrotic syndrome in children (>90% of cases). For this reason, unless clinical and serologic evidence suggests the presence of a disease other than MCG, a kidney biopsy is not performed in children with the nephrotic syndrome unless they do not respond to glucocorticoid therapy. In adults, biopsy series have shown that MCG is the cause of up to 10% to 15% of cases of the nephrotic syndrome, with a greater representation in older patients (≥65 years of age).

The pathophysiology of MCG is not well understood. Similar to FSGS, MCG is a podocytopathy; the presumed model of injury is immunologic, in which a circulating factor (produced by B or T cells) alters podocyte function, resulting in massive proteinuria. Most cases of MCG are primary, but the disease is associated with various conditions, including malignancies (lymphoma, thymoma), medications (NSAIDs, lithium), infections (strongyloides, syphilis, mycoplasma, ehrlichiosis), and atopy (pollen, dairy products).

Clinical Manifestations

The classic presentation of MCG is sudden-onset nephrotic syndrome. Microscopic hematuria is present in 10% to 30% of adult cases. Up to 25% of adults with MCG may also have AKI, more commonly occurring in older patients with hypertension, low serum albumin levels, and heavy proteinuria.

Diagnosis

MCG is diagnosed with kidney biopsy demonstrating normal glomerular histology on light microscopy, negative immunofluorescence staining for immunoglobulin and complement proteins, and complete effacement of the podocyte foot processes on electron microscopy.

Treatment and Prognosis

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis recommends glucocorticoids as first-line therapy for children and adults with MCG, with remission achieved in >90% of children and 80% to 90% of adults. Time-to-response is prolonged in adults compared with children, and adults are not considered to have glucocorticoid-resistant disease until they have not responded to 16 weeks of glucocorticoid therapy. After an initial course of glucocorticoids, patients are subdivided into categories: glucocorticoid-sensitive MCG, glucocorticoid-dependent MCG, infrequently relapsing MCG, frequently relapsing MCG, and glucocorticoid-resistant MCG. Treatment of glucocorticoid-dependent, frequently relapsing, and glucocorticoid-resistant MCG has included calcineurin inhibitors, mycophenolate mofetil, alkylating agents, and rituximab, with variable results.

KEY POINTS

- The classic presentation of minimal change glomerulopathy is sudden-onset nephrotic syndrome.
- Minimal change glomerulopathy is initially treated with glucocorticoids.

Conditions Associated with the Nephritic Syndrome

Rapidly Progressive Glomerulonephritis

Epidemiology and Pathophysiology

Rapidly progressive glomerulonephritis (RPGN; also known as crescentic glomerulonephritis) is not a specific disease but a

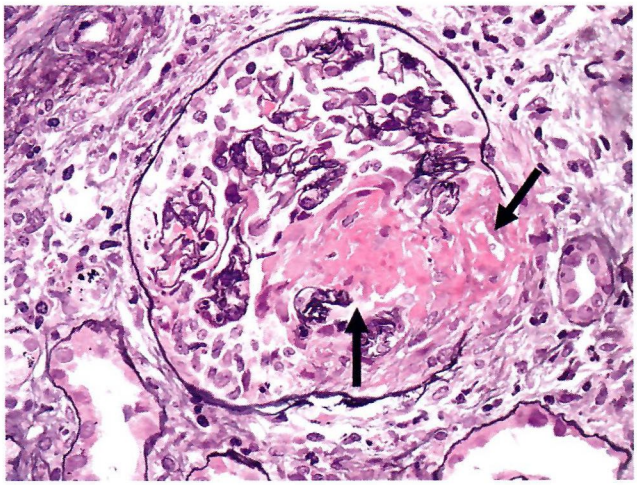


FIGURE 15. A glomerular crescent (*arrows*) signals focal rupture of the glomerular capillary walls.

Courtesy of Glen Markowitz, MD.

clinical entity that can be caused by multiple diseases and manifests as (1) at least a 50% decline in glomerular filtration rate over a short period (usually days to weeks) with (2) pathology findings of extensive glomerular crescents (**Figure 15**). Crescents signal focal rupture of the glomerular capillary walls. This rupture allows accumulation of fibrin and fibronectin in the urinary space, where they activate de-differentiated glomerular parietal epithelial cells to proliferate, surround, and compress the glomerular tuft.

Clinical Manifestations

RPGN typically presents with oliguria and rising serum creatinine along with macroscopic or microscopic hematuria, erythrocyte casts, and varying ranges of proteinuria. AKI can rapidly progress to dialysis dependence.

Diagnosis

The diagnosis of all forms of glomerulonephritis is traditionally made by kidney biopsy, which can distinguish among the three major categories of glomerulonephritis (**Table 22**) and their associated etiologies. Serologic testing (for example, ANCA, anti-glomerular basement membrane antibodies, antinuclear antibodies) aids in the diagnosis. An alternative classification scheme for glomerulonephritis is based on low versus normal complement levels (**Table 23**). Although any form of glomerulonephritis can display an aggressive disease course that would fit the definition of an RPGN, the most common etiologies seen in RPGN cases are ANCA-associated glomerulonephritis, lupus nephritis, and anti-glomerular basement membrane glomerulonephritis.

TABLE 22. Categorization of Glomerulonephritis Based on Immunofluorescence Microscopy Findings

Immunofluorescence Staining Pattern		
Granular	**Pauci-immune**	**Linear**
Lupus nephritis Infection-related GN IgA nephropathy MPGN Cryoglobulinemic GN	ANCA-associated GN	Anti-GBM antibody disease

GBM = glomerular basement membrane; GN = glomerulonephritis; MPGN = membranoproliferative glomerulonephritis.

TABLE 23. Categorization of Glomerulonephritis Based on Serum Complement Levels

Low Serum C3 and/or C4 Levels	Normal Serum C3 and C4 Levels
Lupus nephritis	IgA nephropathy
Infection-related GN	ANCA-associated GN
MPGN	Anti-GBM antibody disease
Cryoglobulinemic GN	

GBM = glomerular basement membrane; GN = glomerulonephritis; MPGN = membranoproliferative glomerulonephritis.

Treatment and Prognosis

Treatment is based on the specific etiology of RPGN. If untreated, RPGN is expected to progress to dialysis dependence in a matter of days to weeks. If treated early, lesions can be reversed, although CKD is often a lingering consequence.

Anti-Glomerular Basement Membrane Antibody Disease

Epidemiology and Pathophysiology

Anti-glomerular basement membrane (anti-GBM) antibody disease is a rare form of RPGN with an incidence of less than one case per million per year. Anti-GBM antibody disease accounts for about 20% of RPGN cases in adults. The lesion is more frequently seen in White patients and has a bimodal age and gender distribution, with peak incidences in young men in the second and third decades of life and in older women in the sixth and seventh decades of life. More than half of patients with anti-GBM antibody disease present with RPGN and pulmonary hemorrhage. About one third of patients present with isolated glomerulonephritis. Notably, up to one third of patients also have concurrent circulating ANCA (usually anti-myeloperoxidase [MPO]) antibodies.

Circulating anti-GBM antibodies target the alpha-3 chain of type IV collagen. When anti-GBM antibodies bind to the GBM, they incite an intense inflammatory response that translates to the typically fulminant nature of this disease, in the absence of treatment.

Clinical Manifestations

The presentation of anti-GBM antibody disease is similar to that of other forms of RPGN, with macroscopic or microscopic hematuria, erythrocyte casts, varying ranges of proteinuria, and usually moderate to severe AKI. Lung

involvement (Goodpasture syndrome) occurs in >50% of patients; hemoptysis can be a presenting symptom, although shortness of breath or cough should also raise suspicion for a pulmonary-renal syndrome even in the absence of hemoptysis.

Diagnosis

Kidney biopsy in anti-GBM disease shows a crescentic glomerulonephritis on light microscopy and pathognomonic linear staining on immunofluorescence for IgG along the glomerular capillaries, indicative of antibodies directed against the GBM. Serologic testing for anti-GBM antibodies is performed at the time of diagnosis. The serologic test is done by indirect immunofluorescence or direct enzyme-linked immunosorbent, with sensitivity ranging from 60% to 100%; therefore, a kidney biopsy to confirm diagnosis is recommended unless contraindicated. Even with a kidney biopsy diagnosis, antibody levels should be measured, as titers can be followed to assess efficacy of therapy.

Treatment and Prognosis

Outcomes in anti-GBM disease are based largely on the degree of AKI at the time of diagnosis and treatment. In an oft-cited series, patients with anti-GBM disease who presented with serum creatinine <5.6 mg/dL (495 µmol/L) had, at 10 years, a <5% overall mortality and a <20% risk for ESKD. In contrast, patients who presented with dialysis-dependent kidney failure had a 35% mortality rate within the first year of diagnosis, and only 8% were able to be taken off dialysis during this time.

Treatment for anti-GBM antibody disease consists of plasmapheresis, pulse glucocorticoids (high doses of intravenous glucocorticoids over a short period of time) followed by oral prednisone, and cyclophosphamide.

ANCA-Associated Glomerulonephritis

See MKSAP 19 Rheumatology for more information on ANCA-associated vasculitis.

Epidemiology and Pathophysiology

ANCA-associated glomerulonephritis (also known as pauci-immune crescentic glomerulonephritis) accounts for more than half of all RPGN cases and has a particularly high prevalence in patients >65 years of age presenting with AKI and active urinary sediment. ANCA are autoantibodies that target proteins within neutrophil granules and monocyte lysosomes. There are two types of vasculitis-associated ANCA: p-ANCA (perinuclear) is directed against the neutrophil enzyme myeloperoxidase (MPO), and c-ANCA (cytoplasmic) is directed against the neutrophil proteinase 3 (PR3).

Clinical Manifestations

Most patients with ANCA-associated glomerulonephritis report a vasculitic prodrome of malaise, arthralgia, myalgia, and flu-like symptoms that can include fever. Kidney involvement can produce dark brown (tea-colored) urine, and laboratory studies will confirm the presence of hematuria, proteinuria, and AKI. Lung and sinus involvement often occurs in ANCA-associated glomerulonephritis, with patients reporting hemoptysis and/or epistaxis.

Diagnosis

Serologic testing for ANCA using enzyme-linked immunosorbent assay is usually performed at the time of presentation if RPGN is suspected. Light microscopy of the kidney biopsy shows a crescentic glomerulonephritis, but immunofluorescence shows a paucity or absence of immune-type deposits. Foci of necrosis or cellular crescents are highlighted by immunofluorescence staining for fibrinogen.

Treatment and Prognosis

The initial treatment of organ-threatening disease is an area of ongoing controversy. Typical induction therapy consists of high-dose glucocorticoids combined with either cyclophosphamide or rituximab. The PEXIVAS study showed no evidence of benefit when plasmapheresis was used for severe kidney failure; in addition, this study reported noninferior results comparing a reduced dose of glucocorticoids versus a standard high-dose regimen. Plasmapheresis should still be used for patients with evidence of alveolar hemorrhage.

After remission is induced, maintenance therapy is usually continued for at least 12 to 24 months using rituximab, azathioprine, or mycophenolate mofetil. Patients with c-ANCA/anti-PR3 have a significantly higher rate of relapse than patients with p-ANCA/anti-MPO, particularly if there is a history of lung or sinus involvement. ANCA-associated glomerulonephritis is associated with an approximately 20% mortality rate within the first year of diagnosis and results in ESKD in up to 25% of surviving patients within the first 4 years after diagnosis.

KEY POINTS

- Rapidly progressive glomerulonephritis is a syndrome characterized by at least a 50% decline in glomerular filtration rate over a short period with histologic findings of extensive glomerular crescents.
- More than half of patients with anti-glomerular basement membrane antibody disease have lung involvement manifesting as hemoptysis, shortness of breath, or cough.
- Treatment of anti-glomerular basement membrane antibody disease consists of pulse glucocorticoids followed by oral prednisone, and cyclophosphamide.
- Plasmapheresis should be used to treat ANCA-associated glomerulonephritis in patients with concomitant pulmonary alveolar hemorrhage.

Immune Complex-Mediated Glomerulonephritis

The glomerulonephritides with granular immunofluorescence microscopy staining patterns all fall under the umbrella category of immune complex-mediated glomerulonephritis, with antigen-antibody complexes depositing in the kidney at various locations and in various patterns (see Table 22). Immune complex deposition activates the classical complement pathway as a co-mediator of glomerular inflammation, injury, and, potentially, scarring. For this reason, most immune complex-mediated glomerulonephritides are associated with low levels of C3 and/or C4 (see Table 23). IgA nephropathy, which usually presents with normal C3 and C4 levels, is an exception because of the chronic, gradual nature of the disease; complement consumption is at a rate slow enough for hepatic production to replace complement proteins.

IgA Nephropathy

Epidemiology and Pathophysiology

IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide, diagnosed in up to 10% of all kidney biopsies done in the United States and approximately one third of all kidney biopsies in Asian countries, where the disease is the leading cause of ESKD. In contrast, IgAN is very rare among patients of African ancestry. IgAN can be diagnosed at any age, particularly because a significant subgroup of patients is asymptomatic, but is most commonly diagnosed in youth or early adulthood, with a 2:1 male-to-female ratio. In the United States, the overall incidence of IgAN is estimated at 2.5 cases per 100,000 person-years, with a prevalence of approximately 80,000 individuals.

In IgAN, there is a defect in IgA1-producing cells leading to hypogalactosylation of the hinge region of IgA1. Blood levels of galactose-deficient IgA1 (Gd-IgA1) are elevated in patients with IgAN. Patients then develop antibodies directed against Gd-IgA1 to form immune complexes that accumulate in the glomerulus.

Clinical Manifestations

IgAN can present with any of the manifestations of the nephritic syndrome. The mildest presentation, seen in up to one third of patients, is asymptomatic microscopic hematuria with or without proteinuria, usually discovered incidentally as part of a routine examination. Recurrent gross hematuria, in which the hematuria occurs in the setting of an upper respiratory infection (synpharyngitic hematuria) is a common presentation in younger patients; it usually portends a benign clinical course with recurrent episodes of gross hematuria without progression to CKD. IgAN can also present as an acute glomerulonephritis or an even more aggressive RPGN, with variable degrees of AKI, hypertension, edema, proteinuria, and hematuria.

Diagnosis

The diagnosis of IgAN may be suspected clinically but can only be made by kidney biopsy showing dominant mesangial immune-deposits of IgA with C3, and occasionally IgG or IgM. In some centers, patients with microscopic hematuria, normal kidney function, and proteinuria <500 mg/24 h are given an empiric diagnosis of IgAN without a biopsy because the disease course is expected to be mild in these cases. In other centers, patients with microscopic hematuria that is deemed to be glomerular in origin (that is, presence of dysmorphic erythrocytes or erythrocyte casts in the urine sediment) elicits a biopsy regardless of kidney function or proteinuria.

Treatment and Prognosis

There are no current standard care therapies for IgAN other than conservative, nonimmunomodulatory therapies. Antiproteinuric therapy using an ACE inhibitor or ARB is a first-line therapy for treating IgAN; it is usually coupled with lipid-lowering therapy and fish oil, although the efficacy of the latter two as specific IgAN therapies is unproven. The use of immunosuppression in IgAN remains controversial. In the United States, it is common for most patients with IgAN who progress to ESKD to have done so despite long-term RAS blockade and at least one course of immunosuppressive therapy.

Approximately one third of patients with IgAN will have a benign long-term course, with continued microscopic hematuria but little to no proteinuria and no evidence of kidney dysfunction. The disease progresses to CKD or ESKD in the remainder of patients, with up to 40% reaching ESKD within 15 years of diagnosis. The Oxford histopathology classification of IgAN provides evidence that advanced disease chronicity, manifesting as >50% tubular atrophy and interstitial fibrosis on kidney biopsy, is the most reliable predictor of progression to ESKD. Among clinical parameters, proteinuria ≥1000 mg/24 h has been shown to be a risk factor for progression.

IgA Vasculitis

IgA vasculitis (also known as Henoch-Schönlein purpura) can present with the classic tetrad of rash, arthralgia, abdominal pain, and kidney disease. Considered a systemic version of IgAN, this vasculitis is often diagnosed empirically in the pediatric setting, because the differential diagnosis of vasculitis in children is extremely limited. In adults, the diagnosis should be confirmed with tissue biopsy (kidney or skin), because the presentation of IgA vasculitis can be mimicked by other forms of vasculitis. Skin biopsy is usually adequate to make the diagnosis when lesions less than 24 hours old in appearance are sampled. Kidney involvement in IgA vasculitis typically is more severe in adults than in children, with higher rates of AKI and the nephrotic syndrome. Treatment includes glucocorticoids and, in cases of associated RPGN, cyclophosphamide.

See MKSAP 19 Rheumatology for more information.

Lupus Nephritis

See MKSAP 19 Rheumatology for more information on systemic lupus erythematosus.

Epidemiology and Pathophysiology

Kidney involvement in systemic lupus erythematosus (SLE), generally termed *lupus nephritis* (LN), is a major contributor to SLE-associated morbidity and mortality. Up to 50% of

patients with SLE will have clinically evident kidney disease at presentation; during follow-up, kidney involvement occurs in up to 75% of patients. LN has been shown to affect clinical outcomes in SLE both directly via target organ damage and indirectly through complications of therapy.

The immune deposits that incite LN are primarily complexes of anti–double-stranded DNA antibodies directed against nucleosomal antigens. A smaller fraction of autoantibodies can also bind directly to chromatin in the GBM and mesangium. These immune complexes, when deposited in the mesangium and subendothelial space, are in direct communication with the systemic circulation. Subsequent activation of the classical complement pathway, triggered by the DNA/anti-DNA antibody complex formation, generates the potent chemoattractants, C3a and C5a, which elicit an influx of neutrophils and mononuclear cells. The pattern on light microscopy is a proliferative glomerulonephritis that can be mesangial (class II), focal endocapillary (class III), or diffuse endocapillary (class IV) (**Table 24**).

TABLE 24. Classification of Lupus Nephritis with Associated Presentation and Treatment Options

ISN/RPS Class	Biopsy Findings	Clinical Features	Treatment	
			Induction Phase	Maintenance Phase
Class I: minimal mesangial LN	No LM abnormalities; isolated mesangial IC deposits on IF and EM	Normal urine or microscopic hematuria	Conservative therapy (e.g., RAS blockade)	Not applicable
Class II: mesangial proliferative LN	Mesangial hypercellularity or matrix expansion with mesangial IC deposits on IF and EM	Microscopic hematuria and/or low-grade proteinuria	Conservative therapy (e.g., RAS blockade)	Not applicable
Class III: focal LN	<50% of glomeruli on LM display endocapillary and/or extracapillary proliferation; mesangial and focal subendothelial IC deposits on IF and EM	Nephritic urine sediment and subnephrotic proteinuria	Pulse IV glucocorticoids followed by tapering doses of oral glucocorticoids *and* IV cyclophosphamide *or* Mycophenolate mofetil	Lowest tolerable amount of oral glucocorticoids *and* Mycophenolate mofetil (tapered down assuming stable disease) *or* Azathioprine (tapered down assuming stable disease)
Class IV: diffuse LN	≥50% of glomeruli on LM display endocapillary and/or extracapillary proliferation; mesangial and diffuse subendothelial IC deposits on IF and EM	Nephritic and nephrotic syndromes; hypertension; reduced kidney function	Pulse IV glucocorticoids followed by tapering doses of oral glucocorticoids *and* IV cyclophosphamide *or* Mycophenolate mofetil	Lowest tolerable amount of oral glucocorticoids *and* Mycophenolate mofetil (tapered down assuming stable disease) *or* Azathioprine (tapered down assuming stable disease)
Class V: membranous LN[a]	Diffuse thickening of the glomerular capillary walls on LM with subepithelial IC deposits on IF and EM, with or without mesangial IC deposits	Nephrotic syndrome	Pulse IV glucocorticoids followed by tapering doses of oral glucocorticoids *and* IV cyclophosphamide *or* Calcineurin inhibitor (cyclosporine or tacrolimus) *or* Mycophenolate mofetil	Lowest tolerable amount of oral glucocorticoids *and* Mycophenolate mofetil (tapered down assuming stable disease) *or* Azathioprine (tapered down assuming stable disease)
Class VI: advanced sclerosing LN	>90% of glomeruli on LM are globally sclerosed with no residual activity	Advanced CKD or ESKD with varying degrees of hematuria and/or proteinuria	Preparation for renal replacement therapy	Not applicable

CKD = chronic kidney disease; EM = electron microscopy; ESKD = end-stage kidney disease; IC = immune complex; IF = immunofluorescence; ISN/RPS = International Society of Nephrology/Renal Pathology Society; IV = intravenous; LM = light microscopy; LN = lupus nephritis; RAS = renin-angiotensin system.

[a]Class V may coexist with class III or class IV, in which case both classes are diagnosed.

Endocapillary proliferation refers to an increased number of inflammatory cells within glomerular capillary lumina, causing luminal narrowing or obliteration. Immune complex deposits in the subepithelial space are separated from contact with the systemic circulation by the GBM, and hence no influx of inflammatory cells occurs into this space. The injury in this class V LN (membranous) is limited to the glomerular epithelial cells, the primary clinical manifestation is proteinuria, and the histologic pattern on light microscopy is similar to primary membranous nephropathy.

Clinical Manifestations

Kidney involvement is uncommon at the time of the initial diagnosis of SLE but will usually manifest with proteinuria and/or microscopic hematuria during the first 3 years of the disease. This eventually progresses to reduction in kidney function. Early in the course of disease, it is unusual for patients to present with decreased kidney function, except for very aggressive cases of LN that present as RPGN. When kidney function is impaired, elevated blood pressure is common.

Diagnosis

The diagnosis of LN is suspected by changes in laboratory parameters (elevated serum creatinine, hematuria and/or proteinuria, low serum complements) but can only be made definitively by kidney biopsy. The classic pattern of LN is an immune complex–mediated glomerulonephritis with a varied pathology that includes six distinct classes of disease (see Table 24). On immunofluorescence microscopy, the glomerular deposits in LN stain dominantly for IgG with co-deposits of IgA, IgM, C3, and C1q in a "full house" pattern. On electron microscopy, tubuloreticular inclusions, which represent "interferon footprints" in the glomerular endothelial cell cytoplasm, are pathognomonic for LN.

Treatment and Prognosis

The current approach to treating LN is guided by histologic findings with appropriate consideration of presenting clinical parameters and the degree of kidney function impairment (see Table 24). Mycophenolate mofetil is equally effective as cyclophosphamide (56% response versus 53% response, respectively) and is less toxic as induction therapy for LN classes III, IV, and V. Fertility is more likely to be preserved with mycophenolate.

Up to 30% of patients with LN will progress to ESKD within 10 years of diagnosis, depending in large part on the response to the initial course of immunosuppression. Severity of disease at the time of diagnosis as well as Black race, Hispanic ethnicity, and socioeconomic status have also been reported to influence outcomes in LN.

Infection-Related Glomerulonephritis

Epidemiology and Pathophysiology

Infection-related glomerulonephritis (IRGN) results from a recently resolved infection or an infection that is ongoing at the time of development of glomerulonephritis. IRGN is preferred to the formerly used term "postinfectious glomerulonephritis," which adequately described classic poststreptococcal glomerulonephritis but did not address the increasingly recognized forms of glomerulonephritis that are manifestations of ongoing infection and nonstreptococcal infectious agents. Diabetes is the most common comorbidity; malignancy, immunosuppression, AIDS, alcoholism, and injection drug use are other recognized comorbidities. Older age is a key risk factor. Patients >65 years of age account for about one third of IRGN cases in the developed world.

The incidence of poststreptococcal glomerulonephritis has declined throughout most of the world because of improvements in infection control and sanitation. The entity, however, remains a health concern in developing countries. In industrialized countries, much of the burden of IRGN has shifted from children to adults, with a decrease in IRGN attributed to streptococcal infections and an increase in IRGN cases associated with *Staphylococcus aureus* and gram-negative bacteria.

In the classic view of the pathogenesis of IRGN, antibodies directed at bacterial antigens form immune complexes in the circulation that subsequently deposit in the glomerulus. Additionally, however, antibodies directed at bacterial antigens planted within glomeruli can result in in situ formation of glomerular immune complexes.

Clinical Manifestations

The variable presentation of IRGN ranges from asymptomatic microscopic hematuria to RPGN. Proteinuria is usually subnephrotic.

In classic poststreptococcal glomerulonephritis, symptomatic patients (typically children) present with an acute nephritic syndrome of hematuria, proteinuria, hypertension, edema, and, in some cases, kidney dysfunction. The urine sediment is active with dysmorphic erythrocytes, erythrocyte casts, and leukocyturia. Hypocomplementemia is common, with decreased C3 in up to 90% of cases. There is usually a latent period (1 to 2 weeks after upper respiratory infections; 2 to 4 weeks after skin infections) between the resolution of the streptococcal infection and the onset of the nephritic syndrome. Serologic markers of a recent streptococcal infection, including elevated antistreptolysin O, antistreptokinase, antihyaluronidase, and antideoxyribonuclease B antibody levels, are often detected. In adults, most cases of IRGN are no longer poststreptococcal, and the glomerulonephritis often coexists with the triggering infection. Low complement levels may be absent in these peri-infectious cases.

Diagnosis

The diagnosis of IRGN can be made clinically in the appropriate setting (for example, classic nephritic presentation with low complements and clear evidence of a recent infection), although the only definitive way to make the diagnosis is by kidney biopsy. The most common finding on light microscopy is a proliferative glomerulonephritis with significant presence of infiltrating neutrophils. On electron microscopy, the classic

finding in poststreptococcal glomerulonephritis is hump-shaped subepithelial electron dense deposits, although these are not required for the diagnosis of IRGN.

Treatment and Prognosis

Treatment is typically supportive and aimed at the infectious etiology, although in some cases with severe proliferative glomerulonephritis on biopsy, a trial of glucocorticoids is used.

In children, prognosis for complete recovery is excellent, and treatment usually is supportive and aimed at the infecting organism. The prognosis of the newly recognized forms of IRGN (for example, due to *S. aureus* and gram-negative organisms) in adults is different, with more patients developing severe kidney dysfunction and progressing to CKD and sometimes ESKD.

Membranoproliferative Glomerulonephritis

Epidemiology and Pathophysiology

Membranoproliferative glomerulonephritis (MPGN) is a rare form of chronic glomerulonephritis diagnosed primarily in children and young adults. The name stems from its pattern of glomerular injury. The entity is divided into immune-complex forms of MPGN (mediated by antigen-antibody interactions triggering the classical complement pathway) versus complement-mediated forms of MPGN (also termed C3 glomerulopathies, because of a hyperactive alternative complement pathway). An immune-complex MPGN, with or without cryoglobulinemia, is the classic form of kidney involvement seen in patients with hepatitis C virus infection. The alternative complement pathway abnormalities that drive the C3 glomerulopathies are either mutations in regulators (for example, complement factor H) or activators (for example, complement factor B) of the alternative pathway, or antibodies directed at regulator or activator complement proteins.

Clinical Manifestations

Although MPGN can rarely present as an acute and severe form of glomerulonephritis, the more common presentation is a chronic glomerulonephritis that initially manifests with microscopic hematuria and subnephrotic proteinuria. As disease progresses, proteinuria can reach nephrotic range, and kidney dysfunction ensues.

Diagnosis

The diagnosis of MPGN is made by kidney biopsy. The distinction between immune-complex and complement-mediated MPGN is based on immunofluorescence microscopy, in which the absence of immunoglobulin staining signals an antibody-independent manner of triggering complement and hence alternative pathway hyperactivity.

Treatment and Prognosis

Currently, treatment of MPGN includes immunosuppression (for example, glucocorticoids) when nephrotic-range proteinuria and/or kidney dysfunction is present. The advent of complement-targeting therapies such as the C5 monoclonal antibody, eculizumab, may bring disease-specific therapy for the complement-mediated forms of MPGN.

The overall prognosis of MPGN as a chronic form of glomerulonephritis is poor, with >50% of patients progressing to ESKD within 15 years of diagnosis.

Cryoglobulinemia

Cryoglobulinemia can be associated with the nephritic syndrome. Of the three types of cryoglobulins, kidney involvement is typically due to type II cryoglobulins.

See MKSAP 19 Hematology for details on cryoglobulinemia; MKSAP 19 Rheumatology for information on cryoglobulinemic vasculitis; and Kidney Manifestations of Deposition Diseases for information on kidney involvement in cryoglobulinemia.

Collagen Type IV-Related Nephropathies

Type IV collagen is an integral component of the GBM. Structural defects in this protein due to genetic variations can result in a hereditary form of glomerulonephritis (Alport syndrome; also termed hereditary nephritis) discussed in more detail in Genetic Disorders and Kidney Disease. In addition, whole exome and whole genome sequencing studies have shown that type IV collagen variants are identified in up to 10% to 15% of adult patients with FSGS.

KEY POINTS

- Treatment of IgA nephropathy consists of conservative therapy using an ACE inhibitor or angiotensin receptor blocker.
- Kidney biopsy is required to diagnose and classify lupus nephritis, which guides therapy.
- Treatment of classes I and II lupus nephritis (LN) includes conservative therapy with an ACE inhibitor or angiotensin receptor blocker; classes III, IV, and V LN require immunosuppressive therapy; and class VI LN should be treated with conservative therapy.
- Infection-related glomerulonephritis results from a recently resolved infection or an infection that is ongoing at the time of development of glomerulonephritis; in industrialized countries, clinical disease is seen more often in adults and is associated with *Staphylococcus aureus* and gram-negative bacteria.
- Treatment of membranoproliferative glomerulonephritis includes immunosuppression when nephrotic-range proteinuria and/or kidney dysfunction is present.

Kidney Manifestations of Deposition Diseases

Overview

Various kidney diseases are associated with deposition of immunoglobulin (Ig) and non-Ig proteins. On electron microscopy, these deposits can be unstructured or organized into fibrils or

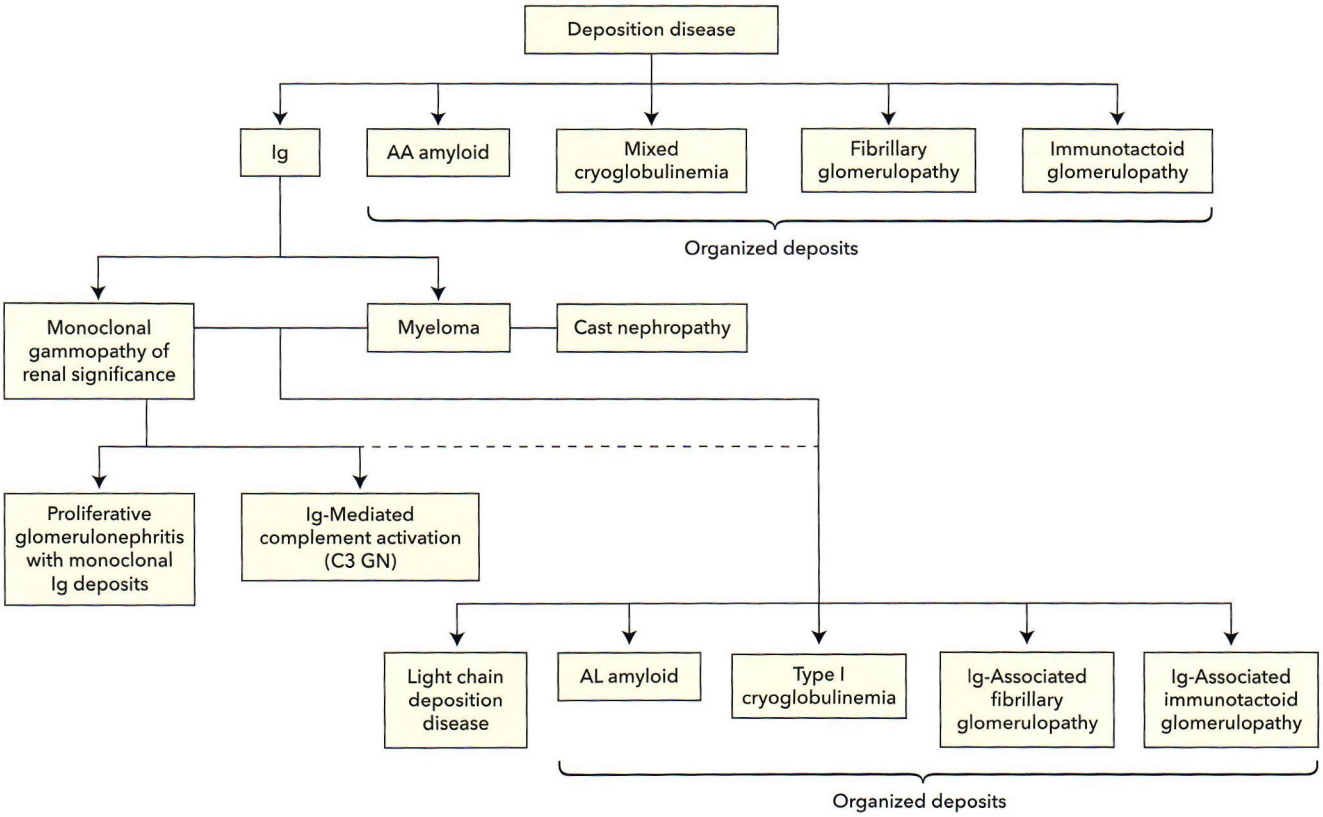


FIGURE 16. Deposition diseases can be divided into five major categories: immunoglobulin (Ig)-related disease, AA amyloid, mixed cryoglobulinemia, fibrillary glomerulopathy, and immunotactoid glomerulopathy. Ig-related disease can be further divided into multiple myeloma and monoclonal gammopathy of renal significance (MGRS). Although some histopathological findings occur more commonly in either multiple myeloma (such as cast nephropathy) or MGRS, most have been reported in either disorder. C3 CN = C3 glomerulopathy (dense deposit disease and C3 glomerulonephritis).

tubules (**Figure 16**). Monoclonal Ig deposits may be caused by amyloidosis, myeloma, Waldenström macroglobulinemia, or chronic lymphocytic leukemia, or by the clonal expansion of Ig-secreting cells that do not meet the strict definition of these disorders but may cause kidney disease, which has been termed *monoclonal gammopathy of renal significance* (MGRS).

The pathological findings associated with monoclonal Ig deposition can include proliferative glomerulonephritis, AL amyloid, type 1 cryoglobulinemia, and, occasionally, fibrillary and immunotactoid glomerulopathy. Polyclonal Ig deposits include mixed cryoglobulinemia, whereas non-Ig proteins contribute to AA amyloid and to most cases of immunotactoid and fibrillary glomerulopathy.

Monoclonal Immunoglobulin-Associated Kidney Disease

A wide array of renal lesions can be caused by clonal expansion of Ig-secreting cells, including frank plasma cell neoplasms. However, paraproteinemia caused by clonal expansion of Ig-secreting cells that do not meet the strict definition of amyloidosis, myeloma, Waldenström macroglobulinemia, or chronic lymphocytic leukemia can be associated with nephrotoxicity. Except for myeloma cast nephropathy seen exclusively with myeloma, all the pathological renal lesions can occur in each of these disorders. Because filtered light chains are endocytosed by proximal tubule cells and are nephrotoxic, patients may present with proximal tubular dysfunction (Fanconi syndrome); common features include glycosuria, phosphaturia, and normal anion gap metabolic acidosis. Creatinine clearance may be normal or abnormal. Renal disorders associated with Ig secretion can be divided into those with organized deposits, such as amyloid, type 1 cryoglobulinemia, fibrillary and immunotactoid glomerulopathy or those in which the deposits are unstructured, such as monoclonal deposition disease and proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID).

Myeloma Cast Nephropathy

Myeloma cast nephropathy occurs in the presence of a markedly increased concentration of free light chains and is always associated with multiple myeloma. Light chains are freely filtered by the glomerulus and combine with secreted Tamm-Horsfall protein, the main protein in urine, to form

obstructing casts. Patients with cast nephropathy present with acute or slowly progressive kidney injury. Serum free light chains are extremely elevated (usually >50 mg/dL [500 mg/L]). Treatment is aimed at reducing the production and concentration of free light chains using chemotherapy. Nephrotoxins, such as contrast media or NSAIDs, and volume depletion should be avoided in these patients. The benefit of plasmapheresis to reduce light chains and improve kidney function is undetermined, but some experts use plasmapheresis as an adjunctive treatment to chemotherapy.

Monoclonal Gammopathy of Renal Significance

Monoclonal gammopathy of renal significance (MGRS) is characterized by kidney damage caused by monoclonal Ig that is secreted by a B cell or plasma cell clone not meeting diagnostic criteria for multiple myeloma or a lymphoproliferative disorder. In the absence of the otherwise unexplained kidney injury, these patients would be thought to have monoclonal gammopathy of unknown significance. All pathological findings associated with the clonal expansion of Ig-secreting cells can be seen in both myeloma and MGRS. The underlying pathology is likely determined by the characteristics of the secreted protein. Entities associated with MGRS include PGNMID, C3 glomerulopathy with monoclonal gammopathy, AL amyloid, type 1 cryoglobulinemia, fibrillary glomerulopathy, and immunotactoid glomerulopathy.

Kidney manifestations of MGRS are usually caused by deposition of monoclonal Ig light chains. Patients can present with nephrotic or subnephrotic proteinuria, hematuria, and elevated serum creatinine.

Kidney biopsy is necessary to make the diagnosis. Further testing may include serum and urine protein electrophoresis with immunofixation, measurement of free light chains, and bone marrow biopsy. Treatment is aimed at eradication of the expanded clonal line.

Monoclonal Immunoglobulin Deposition Disease

Monoclonal light chains (usually κ) or heavy chains can be deposited in the kidney and manifest as proteinuria and kidney failure. Unlike AL amyloid, these proteins do not form β-pleated sheets and do not stain with Congo red. These deposits can be limited to the basement membrane, giving a microscopic appearance similar to that of diabetic nodular sclerosis (light chain deposition disease) or can activate complement and induce a proliferative glomerulonephritis (PGNMID). In some cases, an underlying plasma cell dyscrasia or lymphoproliferative disorder can be identified, but criteria for myeloma or chronic lymphocytic leukemia are often absent.

Amyloidosis

Amyloidosis is a disorder characterized by kidney and other organ injury caused by the deposition of insoluble amyloid proteins that form β-pleated sheets. Although amyloid can be made up of numerous proteins, kidney disease is most commonly caused by AL amyloid or AA amyloid. AL amyloid is composed of monoclonal λ (most commonly) or κ light chains produced by either MGRS or myeloma; AA amyloid is formed by serum amyloid A protein, an acute phase reactant produced in various inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, chronic osteomyelitis, and familial Mediterranean fever. Patients with renal amyloid frequently present with nephrotic-range proteinuria. Less commonly, amyloid can affect only the renal vasculature or tubular interstitium and have minimal or no proteinuria. Treatment is aimed at the underlying disease. See MKSAP 19 Hematology for more information on amyloidosis.

Cryoglobulinemia

Although all three types of cryoglobulinemia can cause kidney disease, kidney involvement occurs most frequently with type II (mixed Ig) cryoglobulinemia and is usually associated with hepatitis C virus infection and small-vessel vasculitis. Patients can present with a nephritic picture: elevated serum creatinine, hypertension, proteinuria, and hematuria. Membranoproliferative glomerulonephritis is usually noted on biopsy. Occasionally, a rapidly progressive glomerulonephritis with crescent formation can occur. A palpable purpuric rash is frequently present on the lower extremities. Treatment is aimed at eradication of the hepatitis C virus. See MKSAP 19 Rheumatology for a discussion of cryoglobulinemic vasculitis. See MKSAP 19 Hematology for a discussion of all three types of cryoglobulinemia.

Fibrillary and Immunotactoid Glomerulopathy

Although rare, both fibrillary and immunotactoid glomerulopathy are increasingly recognized causes of kidney disease. These diseases are caused by glomerular deposition of organized fibrillar or tubular structures that are larger than amyloid and do not stain with Congo red. Proteinuria, frequently in the nephrotic range, and hematuria are common. Although the pathogenesis of these entities is unknown, both have been associated with paraproteinemia. Treatment is usually unsuccessful, and kidney outcomes are poor.

KEY POINTS

- Patients with myeloma cast nephropathy present with acute or slowly progressive kidney injury and have extremely elevated serum free light chains.

(Continued)

KEY POINTS *(continued)*

- Patients with monoclonal gammopathy of renal significance can present with proteinuria, hematuria, and elevated serum creatinine; kidney biopsy is necessary to make the diagnosis.
- Kidney disease in amyloidosis is most commonly caused by AL amyloid composed of monoclonal λ or κ light chains or AA amyloid formed by serum amyloid A protein; patients frequently present with nephrotic-range proteinuria, and treatment is aimed at the underlying disorder.
- Kidney involvement in cryoglobulinemia occurs most frequently with type II (mixed) cryoglobulins; treatment is directed at eradication of commonly associated hepatitis C virus.

Genetic Disorders and Kidney Disease

Genetic Cystic Kidney Disorders

Genetic cystic kidney disorders include autosomal dominant polycystic kidney disease and tuberous sclerosis complex.

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the leading genetic cause of end-stage kidney disease (ESKD) and the fourth leading cause of ESKD. ADPKD manifests as large kidneys with multiple kidney cysts (**Figure 17**). Genetic mutations in *PKD1* and *PKD2*, which encode for proteins that regulate differentiation and proliferation of renal tubular epithelial cells, account for approximately 85% and 15% of cases, respectively. More than 90% of mutations are inherited as an autosomal dominant trait, with spontaneous germline mutations accounting for the remaining cases.

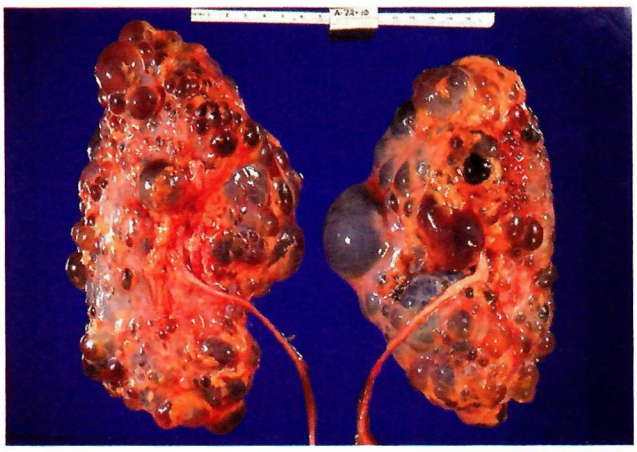


FIGURE 17. Autosomal dominant polycystic kidney disease with multiple bilateral cysts, which replace the normal smooth architecture of the kidneys and lead to markedly increased kidney size. Image from the CDC Public Health Image Library.

Screening and Diagnosis

Ultrasonography is the most common and least costly screening method for ADPKD. Ultrasonography criteria for diagnosing APKD are based on the number of visible cysts that are more than expected for the patient's age. Family history of ADPKD may also be considered. Direct DNA sequencing of the *PKD1* and *PKD2* genes may be used to confirm the diagnosis or, in some cases, is performed in lieu of imaging. Gene linkage testing, which identifies DNA markers in several members of a family, can also be used in patients with a family history of ADPKD.

Clinical Manifestations

Early in the disease course, there are generally no symptoms. Diagnosis is therefore often delayed in patients without a known family history of ADPKD. The first sign of ADPKD is often hypertension; other early signs and symptoms include hematuria (macroscopic or microscopic), pain in the back or abdomen, urinary tract infection, or kidney stones. In patients without a family history, these presentations usually lead to imaging studies that reveal ADPKD. CT or MRI may be used to evaluate for complications in patients with known ADPKD, such as bleeding into a cyst or a suspected kidney stone.

Extrarenal manifestations include hepatic cysts (detected in >80% of patients over their lifetime), mitral valve prolapse, inguinal and umbilical hernias, and intracranial aneurysms (detected in 5% to 10% of patients, with a strong familial pattern).

Management

Patients with ADPKD have a >50% chance of progressing to ESKD by age 70 years. Management primarily focuses on controlling blood pressure with renin-angiotensin system blockade and addressing complications of disease. Vasopressin V2 blockade with tolvaptan slows kidney function decline in adults at risk for rapidly progressing ADPKD. Risk factors associated with rapid disease progression include male sex; onset of hypertension before age 35 years; urologic events (such as gross hematuria, cyst infection, and/or flank pain) before age 35 years; total kidney volume greater than expected for age; truncating *PKD1* mutations; estimated glomerular filtration rate decline >5 mL/min/1.73 m^2 within 1 year; and a family history of ESKD at or before age 58 years. Tolvaptan carries an FDA-mandated safety warning for possible irreversible liver injury. Therefore, patients with ADPKD receiving tolvaptan require frequent laboratory monitoring of liver tests. Patients with ADPKD should be offered screening for cerebral aneurysms by CT or MR angiography, particularly those with a family history of intracranial aneurysm or hemorrhage.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a genetic disorder with mutations in the tumor-suppressing genes *TSC1* or *TSC2* and resulting tumors in many organs, primarily in the brain, eyes, heart, kidney, skin, and lungs. Although TSC is most frequently diagnosed in the pediatric population, mild disease may escape detection until adulthood.

Renal angiomyolipomas occur in 75% of patients with TSC and can be detected by CT, ultrasonography, or MRI. Renal cell carcinoma occurs in 1% to 2% of adults with TSC, and therefore screening with abdominal MRI is recommended every 1 to 3 years. Kidney cysts may also develop. The features of TSC that most strongly affect quality of life are generally associated with the brain: seizures, developmental delay, intellectual disability, and autism.

Surgery or related interventions (radiofrequency ablation, selective arterial embolization) may be required for large (>5 cm) or hemorrhagic renal angiomyolipomas.

KEY POINTS

- Autosomal dominant polycystic kidney disease is characterized by large kidneys with multiple kidney cysts, hypertension, hematuria, pain in the back or abdomen, urinary tract infection, or kidney stones.
- Patients with autosomal dominant polycystic kidney disease should be offered screening for cerebral aneurysm with CT or MR angiography.
- Tolvaptan delays decline in kidney function in adults at risk for rapidly progressive autosomal dominant polycystic kidney disease.
- Kidney manifestations of tuberous sclerosis complex include renal angiomyolipomas, renal cell carcinoma, and cysts.

Genetic Noncystic Kidney Disorders

Genetic noncystic kidney disorders include autosomal dominant tubulointerstitial kidney disease, collagen type IV–related disease, Fabry disease, and apolipoprotein L1 nephropathy.

Autosomal Dominant Tubulointerstitial Kidney Disease

Autosomal dominant tubulointerstitial kidney disease (ADTKD) should be suspected in patients with slowly progressive chronic kidney disease (CKD), a bland urine sediment, small kidneys, and a family history of ESKD. Mutations in *UMOD* are the most commonly identified variants in ADTKD, but variants in *REN, MUC1,* and *HNF1B* have also been identified in families with a history of ADTKD. Gout and anemia that appear earlier than expected for CKD stage have been associated with ADTKD.

Collagen Type IV-Related Nephropathies

Type IV collagen is an integral component of the glomerular basement membrane (GBM). Structural defects in this protein, due to genetic variations, can result in manifestations spanning from GBM thinning to progressive glomerular injury. There is a subgroup of adult patients with focal segmental glomerulosclerosis and type IV collagen mutations (see Glomerular Diseases).

Hereditary Nephritis

Hereditary nephritis (Alport syndrome) is a glomerular disease associated with sensorineural hearing loss and characteristic ocular findings. There are three genetic variants: X-linked (80%), autosomal recessive (15%), and autosomal dominant (5%). Females with the X-linked variant can be asymptomatic carriers or can develop kidney disease depending on activity of the X chromosome in somatic renal cells.

Diagnosis has traditionally been made by kidney biopsy with electron microscopy. In patients with a well-documented family history and microscopic hematuria, diagnosis is increasingly being made by genetic testing. Genetic testing is also the most reliable way to identify heterozygote carriers of type IV collagen mutations. Proteinuria, hypertension, and CKD usually progress to ESKD between the late teenage years and the fourth decade of life. Management is supportive, including blood pressure control with renin-angiotensin system blockade.

Thin Glomerular Basement Membrane Disease

Thin glomerular basement membrane disease (benign familial hematuria) is associated with type IV collagen variants causing GBM thinning, which results in hematuria without significant proteinuria or ensuing glomerulosclerosis. Up to 5% of the population may be affected. Although diagnosis can be made using electron microscopy of kidney biopsy material, thin glomerular basement membrane disease is usually a clinical diagnosis based on benign presentation and course (normal kidney function with microscopic hematuria and little or no proteinuria) and positive family history of similarly benign phenotype (family history of isolated hematuria without kidney failure). The disease has excellent long-term prognosis with rare progression to CKD. Management is supportive.

Fabry Disease

Fabry disease is an X-linked recessive inborn error of glycosphingolipid metabolism caused by deficiency of α-galactosidase A. The enzyme deficiency leads to defective storage of sphingolipid and progressive endothelial accumulation, causing abnormalities in the skin (telangiectasias and angiokeratomas), eye, kidney, heart (premature coronary artery disease), brain, and peripheral nervous system (severe neuropathic pain).

Diagnosis can be made by kidney biopsy but also can be made noninvasively with measurement of leukocyte

enzymatic activity and subsequent genetic testing. Screening for the disease is recommended for family members of affected patients. Enzyme replacement therapy with recombinant human α-galactosidase A is available.

Apolipoprotein L1 Nephropathy

Black persons develop kidney failure at rates four to five times higher than White persons. Genetic variants in the apolipoprotein L1 (*APOL1*) gene explain a large fraction of this health disparity. Two risk alleles for kidney disease (G1 and G2) have been identified in the *APOL1* gene. The transmission of disease risk is consistent with recessive inheritance. High-risk *APOL1* alleles are unusually prevalent possibly because they conferred a survival advantage in sub-Saharan Africa by enhancing innate immunity against African trypanosomal disease (African sleeping sickness).

Persons with a high-risk *APOL1* genotype have an approximately 10-fold increased risk for focal segmental glomerulosclerosis, a 7-fold increased risk for hypertension-attributed ESKD, and, among those with HIV infection, a 29-fold increased risk for HIV-associated nephropathy. In addition, the *APOL1* risk genotype is associated with an increased risk for progression to CKD in other nondiabetic kidney diseases, including lupus nephritis and primary membranous nephropathy.

KEY POINTS

- Autosomal dominant tubulointerstitial kidney disease should be suspected in patients with slowly progressive chronic kidney disease, a bland urine sediment, small kidneys, and a family history of end-stage kidney disease.
- Hereditary nephritis (Alport syndrome) is a glomerular disease associated with sensorineural hearing loss and characteristic ocular findings.
- Thin glomerular basement membrane disease (benign familial hematuria) results in hematuria without significant proteinuria or ensuing glomerulosclerosis, with rare progression to chronic kidney disease.
- High-risk *APOL1* genotype confers increased risk for chronic kidney disease in Black persons.

Acute Kidney Injury

Definition

Acute kidney injury (AKI) is characterized by a sudden decrease in kidney function commonly accompanied by decreased urine output, fluid retention, metabolic acidosis, hyperkalemia, and hyperphosphatemia. The Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group definitions for AKI are described in **Table 25**.

Multiple studies have shown a correlation between more severe stages of AKI and higher mortality and health care utilization. Patients with AKI have an increased risk for developing chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Likewise, patients with preexisting CKD are at an increased risk for developing AKI, a condition known as acute-on-chronic kidney disease.

KEY POINT

- The Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group defines acute kidney injury by any of the following: increase in serum creatinine by ≥0.3 mg/dL (26.5 µmol/L) within 48 hours; an increase in serum creatinine to ≥1.5 times baseline over 7 days; or a urine volume <0.5 mL/kg/h for 6 hours.

Epidemiology and Pathophysiology

The incidence of AKI is estimated to be about 20% of all hospital admissions, of which approximately 10% require dialysis support. AKI affects >50% of patients in the ICU. Mortality varies depending on the severity of AKI, underlying cause, and patient population. Critically ill patients with AKI in the context of multiorgan failure have been reported to have mortality rates >50% when dialysis therapy is required.

AKI can be divided into prerenal, intrinsic, and postrenal causes and can be due to pharmacologic and nonpharmacologic causes (**Table 26** and **Table 27**). Prerenal AKI (prerenal azotemia) is caused by decreased renal perfusion.

TABLE 25. KDIGO Definition of Acute Kidney Injury[a]

Stage[b]	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in S_{Cr} to 1.5 to 1.9 times baseline within 7 days or ≥0.3 mg/dL (26.5 µmol/L) within 48 h	<0.5 mL/kg/h for 6 to 12 h
2	Increase in S_{Cr} to 2 to 2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	Increase in S_{Cr} to 3 times baseline or ≥4.0 mg/dL (353.6 µmol/L) or initiation of RRT or, in patients <18 years, a decrease in eGFR to <35 mL/min/1.73 m^2	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; RRT = renal replacement therapy; S_{Cr} = serum creatinine.

[a]The KDIGO definition is based on the RIFLE (Risk, Injury, Failure, Loss, and ESKD) and AKIN (Acute Kidney Injury Network) criteria.

[b]The definition of acute kidney injury in any stage can be met by fulfilling either the serum creatinine criteria or the urine output criteria. Classification follows correction of volume status and relief of obstruction.

TABLE 26. Pharmacologic Causes of Acute Kidney Injury

Cause	Examples
Prerenal	
Volume depletion	SGLT2 inhibitors, diuretics
Intrarenal/afferent arteriolar vasoconstriction	NSAIDs (including COX-2 inhibitors); amphotericin B; calcineurin inhibitors; iodinated radiocontrast agents
Efferent arteriolar vasodilation	Renin inhibitors; ACE inhibitors; ARBs
Intrinsic	
Acute tubular necrosis	Aminoglycosides; vancomycin, particularly in combination with piperacillin-tazobactam; polymyxins; lithium; amphotericin B; pentamidine; cisplatin; foscarnet; tenofovir; cidofovir; carboplatin; ifosfamide; zoledronate; contrast agents; sucrose; immune globulins; mannitol; hydroxyethyl starch; dextran; synthetic cannabinoids; amphetamines
Acute interstitial nephritis	Etiologies of acute interstitial nephritis are similar to those for chronic tubulointerstitial nephritis. Acute interstitial nephritis may lead to chronic tubulointerstitial nephritis with protracted exposure (see Table 19)
Acute glomerulonephritis	ANCA-associated drugs, such as minocycline and levamisole (veterinary antihelmintic used in some cocaine preparations)
Acute vascular syndromes	Drug-induced TMA: quinine; cancer therapies (gemcitabine, mitomycin, bortezomib, sunitinib); calcineurin inhibitors (cyclosporine, tacrolimus); drugs of abuse (cocaine, ecstasy, intravenous extended-release oxymorphone); clopidogrel; anti-angiogenesis drugs; interferon; mTOR inhibitors
Intratubular obstruction	Crystals: sulfonamides; triamterene; ciprofloxacin; ethylene glycol; acyclovir; indinavir; atazanavir; methotrexate; orlistat; large doses of vitamin C; sodium phosphate purgatives

AKI = acute kidney injury; ARB = angiotensin receptor blocker; COX = cyclooxygenase; mTOR = mammalian target of rapamycin; SGLT2 = sodium-glucose cotransporter 2; TMA = thrombotic microangiopathy.

TABLE 27. Nonpharmacologic Causes of Acute Kidney Injury

Cause	Examples
Prerenal	
Volume depletion	Renal losses; GI fluid losses; hemorrhage; burns
Decreased cardiac output	Heart failure; massive pulmonary embolus; acute coronary syndrome
Systemic vasodilation	Sepsis; cirrhosis; anaphylaxis; anesthesia
Intrinsic	
Acute tubular necrosis	Ischemic: prolonged prerenal AKI from hypovolemia, sepsis, or other causes of hypoperfusion
	Pigment: rhabdomyolysis; intravascular hemolysis
Acute interstitial nephritis	Etiologies of acute interstitial nephritis are similar to those for chronic tubulointerstitial nephritis. Acute interstitial nephritis may lead to chronic tubulointerstitial nephritis with protracted exposure (see Table 20)
Acute glomerulonephritis	Infection-related glomerulonephritis; cryoglobulinemia; IgA; lupus nephritis; renal vasculitis, including ANCA-associated; anti-GBM antibody disease
Acute vascular syndromes	Macrovascular: renal artery occlusion; renal vein thrombosis; polyarteritis nodosa
	Microvascular:
	Disease-associated TMA: HUS; atypical HUS; TTP; HELLP; scleroderma renal crisis; hypertensive emergency
	Atheroembolic disease
Intratubular obstruction	Paraprotein: myeloma; TLS
Postrenal	
Upper tract obstruction	Nephrolithiasis; blood clots; external compression
Lower tract obstruction	BPH; neurogenic bladder; blood clots; cancer; urethral stricture

AKI = acute kidney injury; ANCA = antineutrophil cytoplasmic antibody; BPH = benign prostatic hyperplasia; GBM = glomerular basement membrane; GI = gastrointestinal; HELLP = hemolysis, elevated liver enzymes, and low platelets; HUS = hemolytic uremic syndrome; TLS = tumor lysis syndrome; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.

The integrity of renal tissue is preserved, and tubular and glomerular function remains normal. Intrinsic AKI is caused by structural damage to the renal parenchyma. Postrenal AKI refers to AKI caused by urinary tract obstruction. Prerenal AKI and acute tubular necrosis (ATN) account for approximately 65% to 75% of AKI cases in hospitalized patients.

KEY POINT

- Prerenal acute kidney injury and acute tubular necrosis account for approximately 65% to 75% of acute kidney injury cases in hospitalized patients.

Clinical Manifestations

Patients with AKI can be asymptomatic until extreme loss of kidney function occurs, and patients with mild to moderate AKI are often diagnosed by laboratory studies only. Patients with AKI can also present with oliguria (urine output <500 mL/d or <0.3 mL/kg/h) or anuria (urine output <50 mL/d). Severe AKI can lead to symptoms from volume overload, electrolyte abnormalities, and uremia. Acute uremic symptoms include nausea, vomiting, anorexia, fatigue, muscle cramps, restless legs, confusion, and pruritus. Physical signs may include asterixis. Other manifestations may be bleeding (due to platelet dysfunction), pericarditis, and seizures. Drug or metabolite accumulation and toxicity may complicate the course.

KEY POINT

- Patients with acute kidney injury (AKI) can be asymptomatic until extreme loss of kidney function occurs; severe AKI can lead to symptoms from volume overload, electrolyte abnormalities, and uremia.

Diagnosis

The diagnosis of AKI is based on increased levels of serum creatinine. The most reliable way to distinguish AKI from CKD is knowledge of previous serum creatinine levels; documentation of similarly elevated creatinine levels for ≥3 months suggests that the kidney failure is chronic. However, serum creatinine concentration can be increased by multiple factors independent of kidney function, limiting its specificity for diagnosis of AKI. Serum creatinine is not a sensitive marker of kidney injury in patients with sepsis, liver disease, muscle wasting, or fluid overload and does not provide any information regarding the cause of AKI. Moreover, the rise in serum creatinine is delayed 24 to 36 hours after the onset of injury and decline in glomerular filtration rate (GFR).

The history focuses on identifying vasoactive and potential nephrotoxic medications (including over-the-counter medications, herbal products, and recreational drugs); recent exposure to iodinated contrast agents; other predisposing conditions for AKI; and urinary obstructive symptoms (see Table 26 and Table 27). Physical examination focuses on blood pressure, heart rate, signs of volume status such as jugular venous pressure level and skin turgor, and bladder percussion/palpation. Laboratory evaluation includes blood urea nitrogen (BUN) and creatinine concentrations, electrolytes, complete blood count, and assessment of the urine (urine indices, urinalysis, and microscopic evaluation of the urine sediment) (**Table 28** and **Table 29**).

In patients with oliguria, the fractional excretion of sodium (FE_{Na}) or urea (FE_{Urea}) can help distinguish between prerenal AKI and ATN, with some caveats (see Table 28).

Ultrasonography of the kidneys and bladder should be obtained to exclude urinary tract obstruction and when the underlying cause of AKI is unclear. Kidney size may help distinguish between AKI and CKD, because diminished kidney size with increased cortical echogenicity and/or thinning suggests CKD. Kidney size can be normal in patients with CKD from infiltrative disorders such as diabetes mellitus, HIV-associated nephropathy, amyloidosis, or multiple myeloma. Kidney biopsy should be considered in patients with AKI from no apparent cause, suspected glomerulonephritis, or unexplained systemic disease.

TABLE 28. Diagnostic Findings Differentiating Prerenal Acute Kidney Injury From Acute Tubular Necrosis

Condition	BUN-Creatinine Ratio	Urine Osmolality (mOsm/kg H_2O)	Urine Sodium (mEq/L [mmol/L])	FE_{Na}[a]	FE_{Urea}[b]	Urinalysis and Microscopy
Prerenal	>20:1	>500	<20	<1%[c]	<35%	Specific gravity >1.020; normal or hyaline casts
Acute tubular necrosis	10-15:1	~300	>40	>2%[d]	>35%	Specific gravity ~1.010; pigmented granular (muddy brown) casts and tubular epithelial cells

BUN = blood urea nitrogen; FE_{Na} = fractional excretion of sodium; FE_{Urea} = fractional excretion of urea.

[a] FE_{Na} = (Urine sodium concentration × Plasma creatinine concentration)/(Urine creatinine concentration × Plasma sodium concentration) × 100.

[b] FE_{Urea} = (Urine urea concentration × Plasma creatinine concentration)/(Urine creatinine concentration × Plasma urea concentration) × 100

[c] FE_{Na} can be high in prerenal states with diuretic use, adrenal insufficiency, or metabolic alkalosis.

[d] FE_{Na} can be low in acute tubular necrosis due to contrast-associated nephropathy, pigment nephropathy, glomerulonephritis, or early obstruction.

TABLE 29. Urinalysis and Microscopy in Acute Kidney Injury

Condition	Findings
Acute interstitial nephritis	Mild proteinuria; leukocytes; erythrocytes; leukocyte casts
Acute glomerulonephritis	Proteinuria; dysmorphic erythrocytes; erythrocyte casts
Intratubular obstruction	Crystalluria or Bence-Jones proteinuria[a]
Acute vascular syndromes	Variable hematuria; sometimes mimics acute glomerulonephritis
Postrenal	Variable; bland

[a]Detected by urine immunofixation.

KEY POINTS

- In patients with suspected acute kidney injury, physical examination focuses on blood pressure, heart rate, signs of volume status, and bladder percussion/palpation.
- Ultrasonography of the kidneys and bladder should be obtained for suspected urinary tract obstruction or when the underlying cause of acute kidney injury is unclear.

Causes

AKI can be divided into prerenal, intrinsic, and postrenal causes.

Prerenal Acute Kidney Injury

See Table 26 and Table 27 for the causes of prerenal AKI.

Prerenal AKI (prerenal azotemia) is caused by underperfusion of the kidney with a subsequent decrease in GFR, which is reversible with appropriate therapy. Renal hypoperfusion can occur due to intravascular volume depletion, decreased effective arterial circulation, renal vasoconstriction, and/or medications. Patients may have a history of acute hemorrhage, loss of gastrointestinal fluids, heart failure, decompensated liver disease, sepsis, or recent diuretic or NSAID use. Physical signs of hypovolemia include hypotension, tachycardia, orthostasis, and decreased skin turgor. Patients with heart failure or cirrhosis have physical examination findings supporting these conditions.

In prerenal AKI, the kidney responds by reabsorbing urea, sodium, and water. Laboratory values that support a diagnosis of prerenal AKI are listed in Table 28. Prerenal AKI due to hypovolemia can be distinguished from ATN by the response to a volume challenge. Improvement in urine output (if oliguric) and serum creatinine support the diagnosis of a prerenal etiology.

Drug-induced prerenal AKI typically results from decreased blood flow to the kidney or intraglomerular hemodynamic alterations. Sodium-glucose cotransporter-2 inhibitors or diuretics can cause prerenal AKI from volume depletion. Drugs impairing vasodilatation of the afferent arterioles (such as NSAIDs) or vasoconstriction of the efferent arterioles (such as ACE inhibitors or angiotensin receptor blockers) can cause prerenal AKI, especially in the setting of volume depletion, decreased effective arterial circulation, or preexisting CKD. Calcineurin inhibitors such as cyclosporine and tacrolimus can cause prerenal AKI from afferent arteriolar vasoconstriction.

Management of prerenal AKI includes discontinuing nephrotoxins and increasing renal perfusion by treating the underlying cause, such as correcting volume deficits. If prerenal AKI is not recognized and treated in a timely fashion, prolonged renal hypoperfusion can result in ATN and progressive intrinsic kidney failure.

KEY POINTS

- Prerenal acute kidney injury is caused by underperfusion of the kidney with a subsequent decrease in glomerular filtration rate, which is reversible with discontinuing nephrotoxins and treating the underlying cause.
- Renal hypoperfusion can occur due to intravascular volume depletion, decreased effective arterial circulation, or renal vasoconstriction.

Intrinsic Kidney Diseases

Intrinsic AKI occurs from structural damage to the renal tubules, interstitium, glomerulus, or vascular structures, or from intratubular obstruction (see Table 26 and Table 27).

Acute Tubular Necrosis

ATN due to ischemia, nephrotoxins, and/or sepsis is the most common cause of AKI in hospitalized patients. A history of sepsis, documented protracted hypotension, or nephrotoxin exposure along with assessment of hemodynamics and volume status can aid in the diagnosis. Laboratory values suggestive of ATN are described in Table 28. Urine sediment may be bland but is usually notable for the presence of tubular epithelial cells and coarse granular (muddy brown) casts (**Figure 18**).

Unlike prerenal AKI, ATN does not rapidly improve with restoration of intravascular volume and blood flow to the kidneys. Treatment is supportive because no efficacious pharmacologic therapies exist. Complete or partial renal recovery can take days to weeks. Nonoliguric ATN portends a better renal prognosis than oliguric ATN. Patients with advanced CKD are less likely to recover kidney function compared with patients with baseline normal kidney function or early CKD. Patients with severe ATN who require acute dialysis often recover kidney function but may progress to dialysis-dependent ESKD.

Ischemic Acute Tubular Necrosis

Severe ischemia due to prolonged hypotension, protracted prerenal state, or sepsis can cause ATN (see Table 27). The ischemic injury leads to cytokine release, oxygen-free radical and enzyme production, endothelial activation and leukocyte

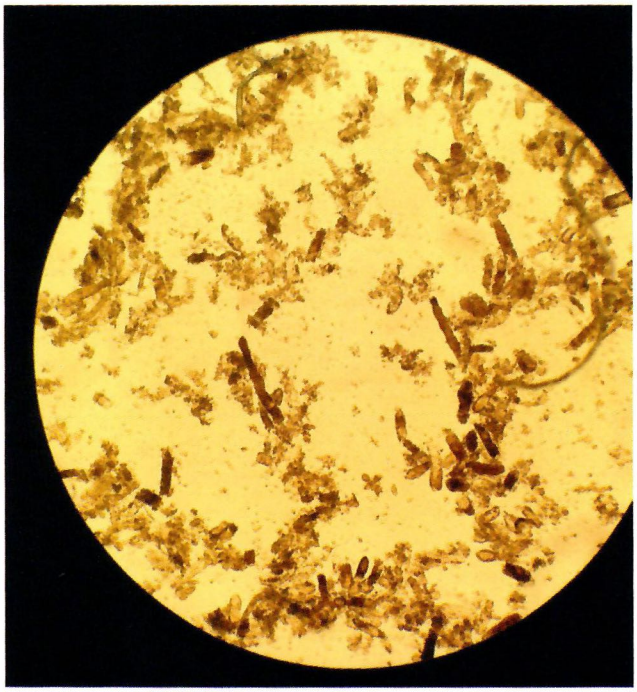


FIGURE 18. Urine sediment showing multiple coarse, granular (muddy brown) casts characteristic of acute tubular necrosis.

adhesion, activation of coagulation, and apoptosis. GFR declines because of renal vasoconstriction, tubular back leak of filtrate into the bloodstream, and tubular obstruction from sloughed cellular debris.

Normotensive ischemic ATN can occur without overt hypotension in conditions with impaired renal autoregulation. These conditions include older age, hypertension, atherosclerotic or renovascular disease, and CKD. Patients with hypertension can develop normotensive ischemic ATN if their blood pressure is decreased to a value lower than what they are accustomed to but within normal range. Management involves treating any volume deficits and decreasing antihypertensive medications to allow the blood pressure to increase to baseline levels.

Drug-Induced Acute Tubular Necrosis

Drug-induced ATN can be a consequence of prolonged hemodynamic alterations or direct tubular injury (see Table 26). The drugs associated with prerenal AKI can cause ATN from prolonged hypoperfusion. Early recognition and prompt discontinuation of the drug are essential for renal recovery. The risk of drug-induced ATN increases in older persons and in patients with decreased effective arterial circulation, CKD, or concomitant nephrotoxin exposure. Hypomagnesemia, hypokalemia, hypophosphatemia, hypocalcemia, and metabolic acidosis may reflect underlying tubular injury.

Osmotic nephrosis is a form of tubular injury due to hyperosmolar substances such as sucrose-containing intravenous immunoglobulin, mannitol, hydroxyethyl starch, dextran, and contrast media. It is characterized by vacuolization and swelling of the renal proximal tubular cells with resultant tubular obstruction and damage.

Contrast agents can cause nonoliguric ATN primarily through renal vasoconstriction and oxygen-free, radical-associated injury. The serum creatinine increases within 24 to 48 hours after contrast administration. Aminoglycosides cause nonoliguric ATN through direct tubular toxicity with an increase in serum creatinine occurring 5 to 7 days after initiation of therapy. Cisplatin causes ATN through direct tubular toxicity, renal vasoconstriction, and inflammation. Amphotericin B causes dose-related AKI through both renal vasoconstriction and direct tubular toxicity and may be associated with nephrogenic diabetes insipidus in addition to the aforementioned tubular defects. Lipid-based preparations decrease the risk for nephrotoxicity. Vancomycin nephrotoxicity occurs in the setting of high trough levels (>15 mg/L), high vancomycin dose (≥4 g/d), prolonged duration of therapy, and/or concomitant nephrotoxic drugs, most notably an aminoglycoside or piperacillin-tazobactam. Certain types of synthetic cannabinoids used as recreational drugs have been associated with ATN.

Pigment Nephropathy

Heme pigment released from myoglobin or hemoglobin can cause AKI through intravascular volume depletion (seen in rhabdomyolysis), renal vasoconstriction, direct proximal tubular injury, and tubular obstruction. Urine heme pigment from myoglobin or hemoglobin causes a positive urine dipstick for blood with the absence of erythrocytes on sediment examination.

In rhabdomyolysis, myoglobin is released in the circulation from damaged skeletal muscle. Major causes of rhabdomyolysis include trauma, drugs and toxins, seizures, metabolic and electrolyte disorders, endocrinopathies (diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, hypothyroidism), and intense exercise, particularly in poorly conditioned individuals. Rhabdomyolysis-induced AKI is more likely to occur with serum creatine kinase levels >5000 U/L. In addition to elevated serum creatine kinase and serum creatinine levels, hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, metabolic acidosis, increased lactate dehydrogenase (LDH) concentration, and increased aspartate and alanine aminotransferase levels can occur. Urinary findings include FE_{Na} <1% (due to renal vasoconstriction), myoglobinuria, and pigmented (red) granular casts.

In addition to correcting the underlying cause, prevention and management of AKI involve aggressive intravenous isotonic fluid resuscitation aimed at maintaining urine output >200 to 300 mL/h. Although limited studies suggest that alkalinization of the urine with intravenous bicarbonate to increase the urine pH >6.5 may prevent tubular cast formation, there is no evidence that such alkaline diuresis either prevents rhabdomyolysis-related AKI or hastens its recovery. If urine alkalinization is used, it should

be closely monitored and discontinued if the patient develops symptomatic hypocalcemia or arterial pH >7.5, or if urine pH does not increase to >6.5 after several hours. Dialysis may be necessary for severe electrolyte and acid-base abnormalities. Most patients have partial or complete renal recovery.

Heme pigment nephropathy is less common and occurs when large amounts of heme pigment are released into circulation due to intravascular hemolysis. Causes include glucose-6-phosphate dehydrogenase (G6PD) deficiency, drug reactions, cardiopulmonary bypass circuits, incompatible blood transfusion, paroxysmal nocturnal hemoglobinuria, malaria, certain poisonings, and snakebites. In addition to elevated serum creatinine concentration, other laboratory abnormalities include anemia, increased LDH, and decreased haptoglobin. Urinary findings include FE_{Na} <1%, hemoglobinuria, and pigmented granular casts. Treatment of hemoglobinuria involves treating the underlying cause as well as volume repletion with intravenous fluids.

KEY POINT

- Acute tubular necrosis due to ischemia, nephrotoxins, and/or sepsis is the most common cause of acute kidney injury in hospitalized patients; a history of sepsis, documented protracted hypotension, or nephrotoxin exposure along with hemodynamic and volume status assessment can aid in the diagnosis.

Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) is a common cause of AKI and is characterized by inflammation and edema of the interstitium. The classic clinical presentation of fever, rash, and peripheral eosinophilia occurs in only 10% to 30% of patients with AIN. Urinary findings can include leukocytes, erythrocytes, and leukocyte casts (see Table 29; see Figure 2). Urine eosinophils are neither sensitive nor specific for AIN, and testing is no longer recommended for diagnosis.

Drug-induced AIN, especially due to antibiotics, proton pump inhibitors, or NSAIDS, is the most common cause of AIN and should be considered in any patient with AKI, a characteristic urinalysis, and history of any drug exposure (see Table 19). Other causes include infections, toxin exposure, and systemic diseases such as autoimmune disorders (see Table 20). Typically, the serum creatinine gradually increases 7 to 10 days after drug exposure but can increase much sooner following repeat exposure of the drug.

Drug-induced AIN from NSAIDs, including selective cyclooxygenase-2 inhibitors, is usually not associated with fever, rash, or eosinophilia and develops 6 to 12 months after drug exposure. AIN from NSAIDs can be associated with the nephrotic syndrome due to minimal change glomerulopathy or membranous nephropathy. The onset of proton pump inhibitor–induced AIN is variable but typically occurs 10 to 13 weeks after exposure. Proton pump inhibitors are thought to be a risk factor for the development of CKD. Chemotherapeutic agents, including ifosfamide, immune checkpoint inhibitors, and pemetrexed, are an underrecognized cause of AIN.

Renal recovery from drug-induced AIN is usually complete if the drug is stopped immediately after the onset of kidney injury but may take weeks to several months. Irreversible interstitial fibrosis (chronic tubulointerstitial nephritis) can develop after 2 weeks of continued exposure. Kidney biopsy should be considered if there is no improvement in kidney function after 5 to 7 days of drug discontinuation. Early glucocorticoid administration may limit damage associated with drug-induced AIN.

KEY POINTS

- Urine eosinophils are neither sensitive nor specific in the diagnosis of acute interstitial nephritis, and testing should not be obtained.
- Drug-induced acute interstitial nephritis is associated with a gradual increase in serum creatinine 7 to 10 days after drug exposure; renal recovery is usually complete if the drug is stopped immediately after the onset of kidney injury.

Acute Glomerulonephritis

Acute glomerulonephritis with AKI results from immune-mediated damage to glomeruli. Urinary findings include proteinuria, dysmorphic erythrocytes, and erythrocyte casts (see Table 29; see Figure 2). Constitutional signs and symptoms are often present. Serologic assays and kidney biopsy identify most causes. Early recognition is extremely important because, without treatment, it can be fatal and result in irreversible kidney damage. See Glomerular Diseases for more information.

Acute Vascular Syndromes

Macrovascular (large and medium vessel) or microvascular (small vessel) disease can cause AKI (see Table 27).

Acute renal arterial occlusion, most often embolic due to atrial fibrillation or atherosclerotic aortic disease, and acute renal vein thrombosis can cause acute renal infarction and present as abdominal or flank pain, elevated serum LDH levels, and hematuria. A notable risk of renal vein thrombosis accompanies the nephrotic syndrome, particularly with membranous nephropathy. Diagnosis may be made by kidney ultrasonography with Doppler. Treatment usually consists of anticoagulation and supportive care.

Patients with atherosclerotic disease who undergo an invasive vascular procedure such as vascular surgery or angiography are at increased risk for atheroembolic-induced AKI (cholesterol emboli). Atheroembolic events can occur spontaneously or several days to weeks after manipulation of the aorta. Plaque rupture causes cholesterol embolization to distal small- and medium-sized arteries, resulting in ischemia with end-organ damage. In addition to the kidneys, atheroemboli can affect the arteries in the skin, muscle, gastrointestinal tract, liver, eyes, and central nervous system. Physical examination findings may include livedo reticularis (lacy network of bluish

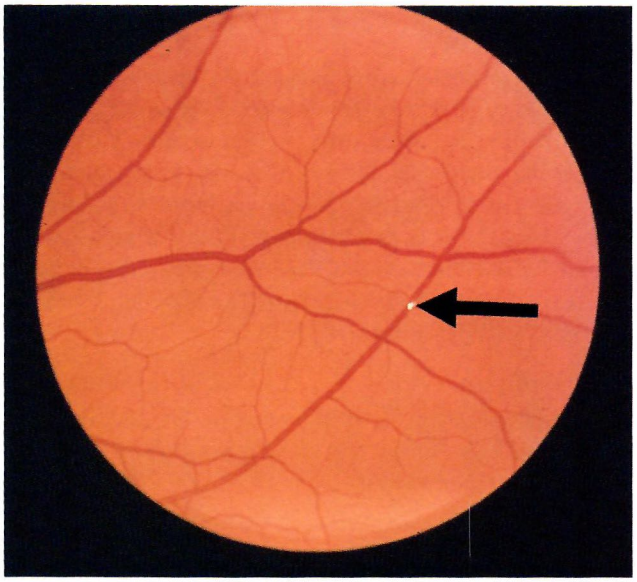


FIGURE 19. A Hollenhorst plaque is a golden-yellow intra-arterial refractile body characteristic of cholesterol emboli. This finding is suggestive of artery-to-artery embolization and may have originated from an ulcerative atherosclerotic plaque located in the internal carotid artery.

red vessels, usually seen on legs) (see MKSAP 19 Rheumatology), Hollenhorst plaques on funduscopic examination (yellow refractile body within arteriole) (**Figure 19**), ulcerations, and blue toes from ischemia (**Figure 20**). Laboratory findings can include low serum complements, peripheral eosinophilia, and eosinophiluria; urinalysis may be unremarkable or can have proteinuria, microscopic hematuria, or erythrocyte casts. Treatment of atheroemboli is supportive and consists of risk factor reduction with aspirin, statins, and management of hypertension. Renal prognosis is poor.

FIGURE 20. Blue toe syndrome. Cholesterol emboli causing necrosis of the skin on the toes.

AKI can also occur from polyarteritis nodosa. It causes microaneurysms of medium size and occasionally small arteries that subsequently rupture, resulting in hemorrhage, thrombosis, and organ ischemia and infarction, including AKI. See MKSAP 19 Rheumatology for more information.

AKI from microvascular disease can present as thrombotic microangiopathy (TMA) with microangiopathic hemolytic anemia, thrombocytopenia, and glomerular capillary thrombosis (see Table 27). See MKSAP 19 Hematology for more information. Urine may show hematuria, erythrocyte casts, and/or proteinuria. Treatment of TMA is based on the underlying cause.

KEY POINTS

- In atheroemboli-induced acute kidney injury (AKI), plaque rupture, especially following a vascular procedure, causes cholesterol embolization resulting in ischemia with AKI and multisystem involvement; treatment is supportive.
- Physical findings of atheroembolic disease include livedo reticularis, digital gangrene, and yellow refractile bodies (Hollenhorst plaques) on funduscopic examination.
- Acute kidney injury from thrombotic microangiopathy (TMA) occurs in thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, preeclampsia, the HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome, hypertensive emergency, scleroderma renal crisis, and complement-mediated TMA (atypical hemolytic uremic syndrome).

Intratubular Obstruction

Intratubular obstruction can cause AKI through precipitation of either protein or crystals within the tubular lumen. Examples include monoclonal light chain deposition in multiple myeloma, calcium oxalate deposition from ethylene glycol ingestion, crystals from drugs, and uric acid from tumor lysis syndrome (see Table 27).

In multiple myeloma, AKI from light chain cast nephropathy is the most common type of kidney disease. Cast nephropathy is due to direct tubular toxicity and obstruction from the precipitation of filtered free light chains. See Kidney Manifestations of Deposition Diseases for more information.

Ethylene glycol intoxication causes AKI from intratubular precipitation of calcium oxalate crystals, which can be seen on urine microscopy. Ethylene glycol should be suspected in a patient with a history of ingestion and whose laboratory studies demonstrate an increased anion gap metabolic acidosis and osmolal gap. Treatment consists of supportive care, the alcohol dehydrogenase inhibitor fomepizole, and hemodialysis if needed. Orlistat, a gastrointestinal lipase inhibitor used to induce clinically significant weight loss by fat malabsorption, has also been associated with intratubular calcium oxalate deposition and AKI. High doses of vitamin C, which is metabolized to oxalate, can also lead to AKI from calcium oxalate precipitation in the tubules.

Drugs associated with crystal-induced AKI are listed in Table 26. Urinary findings include hematuria, pyuria, and crystals. AKI is usually reversed after discontinuation of the drug. Predisposing factors include volume depletion, CKD, and changes in urine pH. Correction of volume depletion with intravenous fluids is critical for both the prevention and treatment of crystal-induced AKI. High-dose intravenous acyclovir can cause acyclovir crystal deposition in the tubules, which can be prevented by prior intravenous fluid administration and slow rate of drug infusion. Because crystals from sulfonamide antibiotics and methotrexate are more likely to form in acidic urine, urinary alkalinization can prevent crystal deposition. Crystals from protease inhibitors can cause AKI from both crystal deposition and nephrolithiasis.

Acute phosphate nephropathy is a potentially irreversible cause of AKI due to phosphate-containing bowel preparations. Although many of these agents have been removed from the U.S. market, acute phosphate nephropathy is occasionally seen in patients, particularly those with preexisting CKD, who have taken sodium phosphate retention enemas. A transient severe increase in serum phosphate in the setting of volume depletion causes acute and chronic tubular injury from tubular and interstitial precipitation of calcium phosphate crystals. AKI can present days to months after exposure. Predisposing factors include volume depletion, CKD, older age, NSAID use, and hypertension treated with ACE inhibitors, angiotensin receptor blockers, or diuretics.

KEY POINT

- Intratubular obstruction causes of acute kidney injury include monoclonal light chain deposition in multiple myeloma; calcium oxalate deposition from ethylene glycol ingestion, orlistat, and high doses of vitamin C; crystals from drugs; and uric acid or calcium phosphate crystal deposition from tumor lysis syndrome.

Postrenal Disease

Postrenal AKI can occur from obstruction anywhere from the renal pelvis to the external urethral meatus (see Table 27). Upper urinary tract obstruction (at the level of the ureters or renal pelvis) must be bilateral or affect a single functioning kidney to cause AKI. Obstruction of urinary flow leads to hydronephrosis and eventual renal parenchymal damage. If postrenal AKI is not treated promptly, the obstruction can predispose the patient to urinary tract infections and urosepsis, and it can also lead to CKD and ESKD.

Postrenal AKI should be suspected in patients with a history of benign prostatic hyperplasia, diabetes, nephrolithiasis, pelvic malignancies, previous retroperitoneal radiation therapy, abdominal or pelvic surgeries, or retroperitoneal adenopathy. Patients can present with anuria, oliguria, polyuria, or normal urine output. Symptoms of lower tract obstruction include abdominal fullness or pain, urinary frequency, urgency, hesitancy, nocturia, overflow incontinence, and incomplete voiding. Acute nephrolithiasis may present with flank pain and hematuria. Presenting signs of obstructive nephropathy may include hypertension. A distended palpable bladder may be evident in bladder outlet obstruction. Serum creatinine is typically elevated at presentation and is sometimes asymptomatic. Hyperkalemia and features of distal renal tubular acidosis may also be evident.

Lower urinary tract obstruction can be diagnosed by an elevated post-void bladder residual volume on ultrasound. Hydronephrosis on kidney ultrasound is present in most causes of obstruction, but false-negative results may occur in the early stages or from encasement of the ureter or kidney, as seen in retroperitoneal disease. Noncontrast CT is indicated for suspected nephrolithiasis. Although less sensitive than CT, kidney ultrasonography is less expensive, has no radiation exposure, and can be used in pregnant women or when CT is unavailable. Treatment focuses on reversing the cause of the obstruction. Renal prognosis depends upon the severity and duration of the obstruction. Renal recovery is generally good if the obstruction is relieved within 1 to 2 weeks.

KEY POINTS

- Postrenal acute kidney injury can occur from obstruction anywhere from the renal pelvis to the external urethral meatus; diagnosis can be made via ultrasonography or noncontrast CT, with generally good renal recovery if the obstruction is relieved within 1 to 2 weeks.
- In patients with postrenal acute kidney injury, the presence of normal urine output or polyuria do not exclude the possibility of obstructive uropathy.

Specific Clinical Settings

Contrast-Associated Nephropathy

Contrast-associated nephropathy (CAN), defined as an increase in serum creatinine levels within 24 to 48 hours of contrast exposure, is a common cause of reversible AKI in the hospital setting. Contrast-induced nephropathy (CIN) includes that subset of CAN in which the kidney injury can be more definitively linked to the contrast. Multiple risk factors have been associated with CAN, but a baseline reduction in estimated GFR (eGFR) appears most important, especially in patients with AKI as well as in patients with CKD and an eGFR <30 mL/min/1.73 m^2.

The AKI tends to be nonoliguric, with an FE_{Na} <1%. The urine sediment may be bland or show classic ATN findings. In addition to advanced CKD, risk factors include diabetic kidney disease, conditions of decreased renal perfusion, high contrast dose, hyperosmolar contrast, and intra-arterial contrast administration. The risk for CAN is lower than previously thought. Use of contrast without a suitable alternative should not be avoided solely on the basis of CAN risk.

Preventive strategies for patients at high risk for CAN include minimizing the amount of contrast and

prophylactically administering intravenous isotonic saline. Prophylactic saline should be administered to all patients with an eGFR <30 mL/min/1.73 m^2 and should be considered for patients with an eGFR of 30 to 44 mL/min/1.73 m^2 who have other risk factors for AKI. There is no role for prophylactic intravenous sodium bicarbonate nor hemodialysis or hemofiltration following contrast exposure. Treatment of CAN is supportive.

Cardiorenal Syndrome

Cardiorenal syndrome (CRS) is a disorder of the heart and kidneys whereby acute or long-term dysfunction in one organ induces acute or long-term dysfunction in the other. CRS is characterized by the triad of concomitant decreased kidney function, diuretic-resistant heart failure with congestion, and worsening kidney function during heart failure therapy. It is seen primarily in heart failure with reduced ejection fraction. The decreased kidney function in CRS is thought to be due to neurohumoral activation, venous congestion and increased renal venous pressure, reduced renal perfusion, and right ventricular dysfunction.

Management is challenging because treatment directed toward improving cardiac function (diuretics, ACE inhibitor/angiotensin receptor blocker, vasodilators, and inotropes) can worsen kidney function. Current evidence does not support the use of ultrafiltration over intensive diuretic management. Decreased kidney function in patients with heart failure is an independent risk factor for all-cause mortality.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a potentially reversible functional kidney impairment that occurs in the setting of portal hypertension due to liver cirrhosis, severe alcoholic hepatitis, or acute liver failure. HRS is characterized by increased renal vasoconstriction and peripheral and splanchnic arterial vasodilation. Tubular function is preserved with the absence of significant hematuria and proteinuria, as well as lack of renal histological changes. Urine sodium concentration is typically <10 mEq/L (10 mmol/L). See MKSAP 19 Gastroenterology and Hepatology for more information.

Type 1 HRS is a clinical diagnosis made after exclusion of other causes of kidney dysfunction. It is characterized by a rise in serum creatinine of at least 0.3 mg/dL (26.5 µmol/L) and/or ≥50% from baseline within 48 hours, bland urinalysis, and normal findings on kidney ultrasound. Patients are often oliguric. Lack of improvement in kidney function after withdrawal of diuretics and 2 days of volume expansion with intravenous albumin supports the diagnosis. Type 2 HRS is defined as a more gradual decline in kidney function associated with refractory ascites.

Patients with HRS have an overall poor prognosis without liver transplantation. General management includes discontinuing diuretics, restricting sodium, restricting water in hyponatremic patients, and searching for precipitating factors. Therapeutic interventions include treatment with vasoconstrictors such as midodrine, octreotide, terlipressin (although not available in the United States or Canada), or norepinephrine, in combination with albumin infusion. Additional interventions may include placement of a transjugular intrahepatic portosystemic shunt in select patients, renal replacement therapy, and liver transplantation. Renal replacement therapy is usually reserved for patients with severe AKI who are liver transplant candidates.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is characterized by the rapid lysis of malignant cells leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and AKI. TLS typically occurs after initiation of chemotherapy in hematologic malignancies with high cell turnover rate, rapid growth rate, or high tumor bulk (acute leukemia or Burkitt lymphoma); however, it can also occur independent of chemotherapy. AKI occurs from deposition of uric acid and/or calcium phosphate crystals in the renal tubules.

Management of TLS requires the initiation of preventive measures in high-risk patients before cytotoxic therapy, as well as the timely initiation of supportive care for patients who develop TLS. Treatment of established TLS includes intravenous volume expansion, urate-lowering therapy, management of hyperkalemia and hyperphosphatemia, and renal replacement therapy in refractory cases. Patients at risk for or presenting with TLS require aggressive volume expansion to achieve a urine output of at least 80 to 100 mL/kg/h. Urinary alkalinization is no longer recommended because the high urine pH can cause an increase in calcium phosphate crystal deposition. Allopurinol or febuxostat, inhibitors of xanthine oxidase, prevent the formation of new uric acid and are recommended as prophylaxis for patients at intermediate risk for TLS (those with highly chemotherapy-sensitive solid tumors); it has no effect on existing serum urate levels. Rasburicase, a recombinant urate oxidase that makes uric acid more soluble in urine with rapid reduction in serum urate levels, is given to patients at high risk for or with TLS. Rasburicase is contraindicated in patients with G6PD deficiency.

Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS) is defined as a sustained elevated intra-abdominal pressure (IAP) associated with new organ dysfunction. IAP >20 mm Hg is commonly associated with ACS, although the absolute pressure measurement is not a sufficient criterion. ACS occurs in the setting of abdominal surgery, trauma, hemoperitoneum, retroperitoneal bleed, ascites, bowel obstruction, ileus, and pancreatitis. It can also occur from capillary leak with concurrent massive fluid resuscitation. Increasing IAP causes hypoperfusion and ischemia of the intestines and other peritoneal and retroperitoneal structures, leading to hemodynamic, respiratory,

neurologic, and kidney impairment. Renal vein compression and renal artery vasoconstriction can cause oliguric AKI.

ACS is diagnosed by measuring IAP; measurement of bladder pressure with an indwelling catheter is the standard methodology. Management includes supportive therapy, abdominal compartment decompression, and correction of positive fluid balance.

KEY POINTS

- Preventive strategies for patients at high risk for contrast-associated nephropathy include minimizing the amount of contrast and expanding volume with intravenous isotonic saline.
- Cardiorenal syndrome is characterized by the triad of concomitant decreased kidney function, diuretic-resistant heart failure with congestion, and worsening kidney function during heart failure therapy.
- General management of hepatorenal syndrome includes discontinuing diuretics, restricting sodium, and treatment with vasoconstrictors in combination with albumin infusion.
- Treatment of established tumor lysis syndrome includes intravenous volume expansion, rasburicase, management of hyperkalemia and hyperphosphatemia, and renal replacement therapy in refractory cases.
- Abdominal compartment syndrome is diagnosed by measurement of bladder pressure with an indwelling catheter.

Management

General Considerations

In most cases of AKI, treatment of the underlying medical condition and discontinuation of nephrotoxic medications lead to improvement in kidney function. No specific pharmacologic therapy is effective in established ATN. Supportive measures include optimizing hemodynamics and renal perfusion, preventing further kidney injury, treating AKI complications, and providing appropriate nutrition. Diuretics can be used for volume overload. Bicarbonate can be administered to correct metabolic acidosis. Dietary potassium, magnesium, and phosphate should be restricted. Phosphate binders may be required to prevent severe hyperphosphatemia. Medication dose adjustments for diminished GFR are necessary to avoid toxicities. An episode of AKI increases the risk for new or worsening CKD. Patients with AKI should be monitored during follow-up for complete recovery of function and/or emergence of CKD, and patients who had preexisting CKD should be evaluated for worsening function.

Renal Replacement Therapy

In some patients with severe AKI, initiation of renal replacement therapy (RRT) may be necessary to manage urgent complications, including hyperkalemia, metabolic acidosis, volume overload refractory to diuretics, uremic manifestations, and dialyzable toxins. Options for RRT for AKI include intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), "hybrid" therapies such as prolonged intermittent renal replacement therapy (PIRRT), and peritoneal dialysis (PD). IHD, CRRT, and PIRRT are extracorporeal therapies that require vascular access in the form of a large-bore, double-lumen central venous catheter; PD requires the placement of an intra-abdominal dialysis catheter and is utilized less frequently for AKI than for ESKD.

IHD, typically delivered 3 to 6 times a week for 3 to 5 hours per session, allows for rapid correction of electrolyte disturbances and rapid removal of drugs or toxins. The main disadvantage of IHD is the risk for hypotension caused by the rapid solute and volume removal. CRRT represents a variety of dialysis modalities developed specifically to manage critically ill patients with AKI who cannot tolerate IHD due to hemodynamic instability. CRRT is administered 24 hours daily and removes solutes and fluid much more slowly than IHD, resulting in better hemodynamic tolerance. PIRRT removes solutes and fluid more slowly than IHD but more quickly than CRRT and is administered 8 to 12 hours daily. Acute PD is not as effective as the other forms of RRT but may be useful when the other types of RRT are unavailable or vascular access cannot be obtained.

Randomized clinical trials have not shown a survival benefit of CRRT over IHD or PIRRT for critically ill AKI patients. CRRT or PIRRT is chosen for patients who are hemodynamically unstable. CRRT is also preferred in patients with cerebral edema because IHD may worsen neurologic status by compromising cerebral perfusion pressure. IHD is favored in patients who need rapid solute removal, such as those with severe hyperkalemia or drug intoxications. Transitions in therapy are common depending on the changing needs of the patient.

Studies of the timing of RRT initiation in critically ill patients and those with sepsis demonstrate no mortality benefit to early introduction of RRT compared with based on usual clinical criteria. In fact, the latter strategy was sometimes associated with avoiding the need for RRT.

KEY POINTS

- In most cases of acute kidney injury, treatment of the underlying medical condition and discontinuation of nephrotoxic medications lead to improvement in kidney function.
- Patients with acute kidney injury should be evaluated in follow-up to monitor for complete recovery of function and/or emergence or worsening of chronic kidney disease.
- Renal replacement therapy is used to manage the urgent complications of severe acute kidney injury, including hyperkalemia, metabolic acidosis, volume overload refractory to diuretics, uremic manifestations, and dialyzable toxins.

(Continued)

KEY POINTS *(continued)*

HVC
- There is no proven benefit to early administration of renal replacement therapy versus timing based on usual clinical criteria in critically ill patients or those with sepsis.

Kidney Stones

Overview

Approximately 7% to 11% of the U.S. population will develop nephrolithiasis, and 50% will have recurrent disease. Risk factors for developing kidney stones include male sex, older age, White race, obesity, diabetes mellitus, the metabolic syndrome, decreased fluid intake, chronic diarrheal states, and Roux-en-Y gastric bypass. Previous antibiotic use is also associated with an increased risk for stone formation.

Clinical Manifestations

Although kidney stones may be asymptomatic and diagnosed as an incidental finding on imaging, the typical presentation is waxing and waning "colicky" flank pain that radiates to the groin. Nausea, vomiting, and dysuria may also be present. Microscopic hematuria is usually noted, although its absence does not exclude a stone.

Similar symptoms may be present in pyelonephritis and acute abdominal processes, which need to be considered. In addition, the ureteral passage of blood clots can cause renal colic pain.

KEY POINT

- Kidney stones typically present with waxing and waning "colicky" flank pain that radiates to the groin; nausea, vomiting, and dysuria may also be present.

Diagnosis

Nephrolithiasis should be considered in all patients who present with flank pain. Costovertebral angle tenderness may be present. Microscopic examination of the urine for hematuria, leukocytes that may indicate infection, pH measurement, and crystals is mandatory, but findings are nonspecific. The presence of crystals may help to identify the type of stone (see Table 3). A complete blood count and complete metabolic panel should be obtained to exclude infection and acute kidney injury, and to screen for common metabolic causes of stone disease.

Definitive diagnosis is made with imaging. Noncontrast helical CT is the gold standard modality because of its high sensitivity and specificity. Although less sensitive than CT, kidney ultrasonography is less expensive, has no radiation exposure, and can be used in pregnant women or when CT is unavailable. Plain abdominal radiography has a low sensitivity and should not be ordered except to follow the stone burden in established disease.

KEY POINT

- Noncontrast helical CT is the gold standard modality to diagnose nephrolithiasis; kidney ultrasonography can be used in pregnant women or when CT is unavailable.

Types of Kidney Stones

See **Table 30** for details on kidney stones and Table 3 for images of crystals.

TABLE 30. Kidney Stone Risk Factors and Therapy

Stone Type	Risk Factors	Therapy
Calcium oxalate	Clinical: hyperparathyroidism; fat malabsorption; excessive vitamin D or C intake	Increase fluids
		Decrease sodium intake
		Decrease animal protein intake
	Biochemical: hypercalciuria; hyperoxaluria; hypocitraturia	Maintain adequate dietary calcium
		Low oxalate diet
		Thiazide diuretics
		Potassium citrate or bicarbonate
Calcium phosphate	Clinical: distal renal tubular acidosis; hyperparathyroidism; carbonic anhydrase inhibitors	Increase fluids
		Decrease sodium intake
		Decrease animal protein intake
	Biochemical: elevated urine pH; hypercalciuria; hypocitraturia	Maintain adequate dietary calcium
		Thiazide diuretics
		Treat hyperparathyroidism
		Potassium citrate or bicarbonate
Uric acid	Clinical: the metabolic syndrome; gout; diarrheal illnesses; metabolic acidosis	Increase fluids
		Potassium citrate or bicarbonate
		Acetazolamide
	Biochemical: low urine pH; hyperuricosuria	Allopurinol
Struvite	Clinical: chronic urinary tract infections with urea-splitting organisms	Treat infection
		Urologic intervention
	Biochemical: elevated urine pH	
Cystine	Clinical: strong family history; young age at onset	Increase fluids
		Potassium citrate or bicarbonate
	Biochemical: elevated urine cystine; low urine pH	Acetazolamide
		Penicillamine
		Tiopronin

Calcium

Eighty percent of kidney stones contain calcium; most are composed of calcium oxalate, and the remainder are composed of calcium phosphate or a combination of the two.

Calcium oxalate stones are associated with hypercalciuria, hyperoxaluria, and hypocitraturia. Up to 50% of patients with recurrent stones have elevated 24-hour urine calcium levels. This may be secondary to elevated serum calcium as seen in hyperparathyroidism, sarcoidosis, or excessive vitamin D intake, but is more frequently idiopathic. Hyperoxaluria can be primary or can occur secondary to increased dietary oxalate intake or absorption; decreased calcium in the gastrointestinal tract (as occurs with a low-calcium diet); or binding of calcium to fatty acids (as occurs with malabsorption syndromes). It can also occur after Roux-en-Y gastric bypass surgery or with use of the weight loss drug orlistat, which allows increased absorption of oxalate. High intake of vitamin C, which is metabolized to oxalate, can also cause hyperoxaluria. Because citrate prevents calcium crystal formation, low urine levels are associated with increased stone formation. Urinary citrate is decreased in the presence of metabolic acidosis, as occurs with chronic diarrhea and distal renal tubular acidosis.

Calcium phosphate stones occur when there is persistently elevated urine pH and are associated with distal renal tubular acidosis, hyperparathyroidism, and carbonic anhydrase inhibitors that increase urine pH, such as acetazolamide or topiramate.

Struvite

Struvite stones occur in the presence of urea-splitting bacteria such as *Proteus*, *Klebsiella*, or, less frequently, *Pseudomonas* species. These bacteria split urea into ammonium, which markedly increases urine pH and results in the precipitation of magnesium ammonium phosphate (struvite). The pH of the urine will be >7.5. Struvite stones commonly produce staghorn calculi (stones that bridge two or more renal calyces) and occur most frequently in older women with chronic urinary tract infections. Because struvite stones are large and grow rapidly, they do not pass into the ureter to cause pain typical of smaller stones. Signs and symptoms typically are related to the underlying infection. Struvite staghorn calculi should be removed to avoid increased morbidity from sepsis and end-stage kidney disease.

Uric Acid

Uric acid stones (<10% of stones) develop in the presence of a persistently acidic urine, which decreases the solubility of uric acid. In addition, some individuals overproduce urate, resulting in increased urine uric acid; both gout and hyperuricemia are associated with uric acid stones but are not always present. Chronic diarrhea, resulting in metabolic acidosis and low urine volume, is a common cause of uric acid stones. The metabolic syndrome is also associated with uric acid stone formation. Uric acid stones are radiolucent but are visualized on ultrasound and CT.

Cystine

Cystine stones (1%–2% of stones) result from cystinuria, an autosomal recessive disease that presents at a young age. These stones are recognized by characteristic hexagonal crystals in the urine (see Table 3). They may also form staghorn calculi and are less radio-opaque than calcium-containing stones.

KEY POINTS

- Eighty percent of kidney stones contain calcium; most are composed of calcium oxalate, which is associated with hypercalciuria, hyperoxaluria, and hypocitraturia.
- Staghorn calculi are the result of infection by urea-splitting bacteria such as *Proteus*, *Klebsiella*, or, less frequently, *Pseudomonas* species and can lead to both sepsis and end-stage kidney disease.
- Uric acid stones are radiolucent and are associated with chronic diarrhea, the metabolic syndrome, and gout.
- Cystine stones result from cystinuria, an autosomal recessive disease that presents at a young age.

Management

Acute management of symptomatic nephrolithiasis is aimed at pain management and facilitation of stone passage. Pain can be relieved by NSAIDs and opioids as needed. Stone passage decreases with increasing size. Only 50% of stones >6 mm will pass, generally within 2 weeks, and stones >10 mm are extremely unlikely to pass spontaneously. The data concerning the use of medications such as tamsulosin, nifedipine, silodosin, and tadalafil to enhance stone expulsion are controversial. But because there are few adverse effects attributed to these medications, many experts recommend their use.

Urologic intervention is required in all patients with evidence of infection, acute kidney injury, intractable pain, and stones that fail to pass. This may necessitate shock wave lithotripsy, ureteroscopy with laser ablation, or percutaneous nephrolithotomy.

Patients should strain their urine to collect stone fragments for chemical analysis if the type of stone is unknown. In addition to the initial evaluation previously described, a 24-hour urine collection for measurement of volume, calcium, oxalate, citrate, uric acid, and sodium should be obtained from all patients with recurrent stones.

Increased fluid intake is the most important intervention to prevent recurrent disease regardless of stone composition. Urine output should be >2500 mL/d to decrease urine solute concentration.

Other interventions should be based on findings in the metabolic evaluation and stone analysis (see Table 30). If hypercalciuria is present, calcium excretion can be decreased by the use of thiazide diuretics. Because calcium excretion parallels sodium excretion, limiting sodium intake will also lower urine calcium. Limiting animal protein may also have a beneficial effect on lowering urine calcium.

Unless excessive, dietary calcium should not be restricted because this will increase oxalate absorption. Oxalate excretion can be decreased by limiting foods high in oxalate such as nuts, cocoa, spinach, rhubarb, and beets. Potassium citrate or potassium bicarbonate will increase urinary citrate excretion, which helps prevent crystallization. An additional benefit of potassium citrate is a decrease in renal calcium excretion, possibly related to preventing calcium release from bone.

In patients with uric acid stones, management consists of increasing the solubility of uric acid by alkalinizing the urine with potassium citrate or bicarbonate; allopurinol can be beneficial if uric acid excretion is elevated.

In patients with cystine stones, urine output should be maintained at >3000 mL/d to decrease solubility of urinary cystine. Urinary cystine excretion can be further reduced by limiting sodium intake and by alkalizing the urine to a pH >7.0.

Struvite stones typically require urologic intervention. Before any surgical procedure, it is important that active infection be treated with antibiotics to avert sepsis. To prevent recurrent stone formation, all stone fragments must be removed from the kidney. In patients unable to undergo surgery, the urease inhibitor acetohydroxamic acid may reduce urine alkalinity and decrease stone growth; however, this is best used as an adjunct to urologic intervention.

KEY POINTS

- Acute management of symptomatic nephrolithiasis includes pain management and facilitation of stone passage.
- Urologic intervention is required in all patients with evidence of infection, acute kidney injury, intractable pain, and stones that fail to pass.
- Increased fluid intake to >2500 mL/d is the most important intervention to prevent recurrent kidney stones, regardless of stone composition.

The Kidney in Pregnancy

Normal Physiologic Changes in Pregnancy

Pregnancy is a state of volume expansion and vasodilation. Sodium and water retention increase plasma volume, augmenting renal blood flow and increasing glomerular filtration rate (GFR) by up to 50%. With the GFR increase, serum creatinine levels decrease. Therefore, high normal serum creatinine levels may indicate significant kidney impairment. Despite the volume expansion, blood pressure begins to decrease in the first trimester and reaches the nadir in the second trimester due to peripheral vasodilation.

Proteinuria increases, with the upper limit of normal increasing from 100 mg/24 h in nonpregnant to approximately 200 mg/24 h in pregnant women. Values >300 mg/24 h are considered abnormal. Prepartum proteinuria may also worsen during pregnancy, making pregnancy-related changes difficult to distinguish from a flare of an underlying kidney disease or development of preeclampsia.

Because of increased renal vascular and interstitial volume, kidney size may increase by 1 to 1.5 cm. Physiologic hydronephrosis and hydroureter, due in part to external compression of the ureters, are common in pregnancy, increase as pregnancy advances, and may take weeks to resolve postpartum. The dilated collecting system can lead to urinary stasis, which increases the risk for pyelonephritis. Therefore, screening for asymptomatic bacteriuria at least once in early pregnancy is recommended, and treatment is indicated. See MKSAP 19 Infectious Disease for more information.

Chronic respiratory alkalosis due to progesterone-induced hyperventilation commonly decreases P_{CO_2} to 27 to 32 mm Hg (3.6-4.3 kPa). Renal compensation results in decreased serum bicarbonate levels between 18 to 20 mEq/L (18-20 mmol/L), with a serum pH of approximately 7.45.

Changes in antidiuretic hormone response to osmolality (reset osmostat) cause mild hyponatremia (decrease in serum sodium of 4 to 5 mEq/L [4-5 mmol/L]) with a decrease in serum osmolality by 8 to 10 mOsm/kg H_2O. No treatment is indicated. Rarely, transient gestational diabetes insipidus can develop due to excessive metabolism of antidiuretic hormone by placental vasopressinase.

KEY POINTS

- Pregnancy is associated with increased glomerular filtration rate with decreased serum creatinine and increased proteinuria.
- Screening for asymptomatic bacteriuria at least once in early pregnancy is recommended, and treatment is indicated.
- Mild hyponatremia from a reset in antidiuretic hormone response to hypo-osmolality occurs normally during pregnancy and requires no management.

Hypertension in Pregnancy

Chronic Hypertension

The American College of Obstetricians and Gynecologists (ACOG) defines chronic hypertension as a systolic blood pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg starting before pregnancy or before 20 weeks of gestation or persists longer than 12 weeks postpartum. It is associated with worse maternal and fetal outcomes. Hypertension first recognized during pregnancy before 20 weeks' gestation usually indicates chronic hypertension. The lower BP measurements associated with physiologic changes of pregnancy can mask hypertension during the first trimester.

ACOG recommends treating persistent systolic BP ≥160 mm Hg or diastolic ≥110 mm Hg in pregnant women

with chronic hypertension, and maintaining BP at 120-159/80-109 mm Hg. These goals remain controversial, with some suggesting lower targets, especially in patients with chronic kidney disease or other comorbidity. Antihypertensive treatment reduces the risk for progression to severe hypertension by 50% but has not been shown to prevent preeclampsia, preterm birth, being small for gestational age, or infant mortality. Any evidence of end-organ damage requires treatment, regardless of severity of hypertension. Importantly, all antihypertensive medications cross the placenta.

Renin-angiotensin system agents (ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors) are all contraindicated because of teratogenicity, even early in pregnancy, and should be stopped before conception (in those planning pregnancy). If conception has already occurred, they should be stopped immediately and the mother counseled regarding possible fetal effects.

First-line therapy includes methyldopa and labetalol, which have been used safely and extensively in pregnancy. Methyldopa monotherapy may be insufficient, in which case it can be replaced with labetalol. Calcium channel blockers can be added; nifedipine has been used most extensively. The β-blockers metoprolol and pindolol have also been used in pregnancy, but atenolol and propranolol may have adverse fetal effects. Diuretics must be used with caution because they may induce oligohydramnios if started during pregnancy.

ACOG also recommends low-dose aspirin (81 mg/d) for all pregnant women with chronic hypertension to be taken from weeks 12 to 28 of gestation.

Gestational Hypertension

Gestational hypertension first manifests after 20 weeks of pregnancy without proteinuria or other end-organ damage (features of preeclampsia) and resolves within 12 weeks of delivery. Preeclampsia occurs in approximately one third of cases. Hypertension persisting beyond 12 weeks' postpartum is considered chronic hypertension. Gestational hypertension can recur in subsequent pregnancies and is associated with an approximately fourfold risk for development of chronic hypertension.

KEY POINTS

- Chronic hypertension precedes pregnancy or is present before 20 weeks' gestation and persists longer than 12 weeks' postpartum.
- The American College of Obstetricians and Gynecologists recommends treating persistent systolic blood pressure (BP) ≥160 mm Hg or diastolic ≥110 mm Hg in pregnant women with chronic hypertension, and maintaining BP at 120-159/80-109 mm Hg.
- Renin-angiotensin system agents (ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors) are contraindicated in pregnancy because of teratogenicity.

(Continued)

KEY POINTS *(continued)*

- First-line therapy of chronic hypertension in pregnancy includes methyldopa and labetalol.
- Gestational hypertension first manifests after 20 weeks of pregnancy without proteinuria or other end-organ damage and resolves within 12 weeks of delivery.

Acute-Onset Severe Hypertension

The 2019 ACOG recommendations on emergent therapy for acute-onset severe hypertension during pregnancy and the postpartum period define acute-onset severe hypertension as systolic BP ≥160 mm Hg and/or diastolic BP ≥110 mm Hg. Such severe BP may occur in the setting of previously controlled chronic hypertension, as a component of preeclampsia, in the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, or de novo in women without these complications. Women with acute-onset severe hypertension persisting >15 minutes require emergent therapy, most typically with intravenous labetalol or hydralazine, or with immediate-release oral nifedipine.

The target goal of treatment is not normalization of BP but rather BP of 140-150/90-100 mm Hg. Maternal and fetal monitoring is advised. Maternal BP should be controlled before delivery. Magnesium sulfate is also advised as emergent therapy for seizure prophylaxis and should be given to women with acute-onset severe hypertension regardless of other signs of preeclampsia or eclampsia.

Preeclampsia

Preeclampsia is defined by new-onset hypertension and proteinuria (urine collection ≥300 mg/24 h or urine protein-creatinine ratio ≥300 mg/g) that occurs after 20 weeks of pregnancy (**Table 31**). New-onset hypertension with new-onset end-organ damage (such as liver or kidney injury, pulmonary edema, cerebral or visual symptoms, or thrombocytopenia) is also diagnostic of preeclampsia. Severe preeclampsia is identified by persistent systolic BP >160 mm Hg or diastolic BP >110 mm Hg and end-organ damage. Eclampsia is the presence of seizures in context of preeclampsia without other cause. The HELLP syndrome is a life-threatening state complicating 10% to 20% of preeclampsia cases. Risk factors for preeclampsia include prior preeclampsia (with an approximate 20% recurrence rate), nulliparity, diabetes mellitus, advanced maternal age, multiple gestation, and family history. The pathophysiology of preeclampsia is poorly understood. Abnormal placental vascular development and generalized endothelial dysfunction occur.

Symptoms of preeclampsia include rapid weight gain due to edema, nausea, vomiting, abdominal pain (particularly concerning if in the right upper quadrant, signifying possible HELLP syndrome), headaches, altered mental status, and blurred vision. If untreated, preeclampsia ultimately leads to maternal end-organ damage and fetal growth retardation, and it may cause maternal and/or fetal death.

TABLE 31. Diagnostic Criteria for Preeclampsia

Blood pressure	≥140 mm Hg systolic or ≥90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure
	≥160 mm Hg systolic or ≥110 mm Hg diastolic; hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	≥300 mg/24 h urine collection (or this amount extrapolated from a timed collection)
	or
	Urine protein-creatinine ratio ≥300 mg/g
	Dipstick reading of 2+ (used only if other quantitative methods are not available)
Or, in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:	
Thrombocytopenia	Platelet count <100,000/μL (100 × 10^9/L)
Kidney dysfunction	Serum creatinine concentrations >1.1 mg/dL (97.2 μmol/L) or a doubling of the serum creatinine concentration in the absence of other kidney disease
Impaired liver function	Elevated blood concentrations of liver aminotransaminases to twice the normal concentration
Pulmonary edema	–
Cerebral or visual symptoms	–

With permission from American College of Obstetricians and Gynecologists' Committee on Practice Bulletins. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. Obstet Gynecol. 2020;135:e237-e60. [PMID: 32443079] doi:10.1097/AOG.0000000000003891

Low-dose (81 mg/d) aspirin started after 12 weeks of pregnancy reduces the rate of preeclampsia in women at high risk. Antihypertensive medications do not prevent preeclampsia but reduce complications of stroke, heart failure, and kidney injury. Most experts initiate treatment at BP >150-160/100-110 mm Hg, although there is no consensus.

Emergent management of acute-onset severe hypertension of preeclampsia includes intravenous labetalol or hydralazine, or oral short-acting nifedipine, and is indicated before delivery.

Definitive treatment of preeclampsia is delivery. Maternal risk for complications diminishes in the hours after delivery, although proteinuria may take months to resolve. Maternal benefits must be weighed against neonatal risks for a preterm delivery, but severe preeclampsia is an indication for immediate delivery regardless of gestational age. Mild preeclampsia may be managed conservatively, with maternal and fetal monitoring and treatment of hypertension. In all cases, close attention to hypertension is recommended in the postpartum period.

KEY POINTS

- Preeclampsia is defined by new-onset hypertension and proteinuria that occurs after 20 weeks of pregnancy.
- Low-dose (81 mg/d) aspirin started after 12 weeks of pregnancy reduces rates of preeclampsia in women at high risk.
- Emergent management of acute-onset severe hypertension of preeclampsia includes intravenous labetalol or hydralazine, or oral short-acting nifedipine.
- Definitive treatment of preeclampsia is delivery.

Chronic Kidney Disease in Pregnancy

Chronic kidney disease and a serum creatinine level >1.4 mg/dL (124 μmol/L) increases the risk of kidney and pregnancy-associated complications. Proteinuria may also increase risk, but an elevated serum creatinine has greater impact. Complications include preeclampsia, acute kidney injury, progression of chronic kidney disease, end-stage kidney disease, preterm delivery, gestational hypertension, intrauterine growth retardation, and fetal loss. Preconception counseling regarding these risks is essential.

Pregnancy is uncommon in women receiving dialysis, which is associated with infertility. Levels of β-human chorionic gonadotropin may increase in nonpregnant dialysis patients; therefore, ultrasonography is usually necessary to confirm pregnancy. Pregnancy in the context of dialysis is associated with very high risk of preeclampsia and fetal loss, although live birth rates have improved to 60% to 80%. To optimize fetal outcomes, hemodialysis frequency and dose are increased to improve BP and volume status.

Pregnancy in women with kidney transplants is more common than in those receiving dialysis. Outcomes are improved with better allograft function (serum creatinine <1.5 mg/dL [132.6 μmol/L]) and stable immunosuppression; transplant patients should await 1 to 2 years with a stable allograft before attempting conception. No immunosuppressive medication has been extensively studied in pregnancy, and all have some associated risk. Although calcineurin inhibitors (tacrolimus and cyclosporine) have been used safely, mycophenolate mofetil is teratogenic and needs to be replaced 3 to 6 months before conception with azathioprine, which has an

extensive history of use in pregnancy. Sirolimus is contraindicated because of fetal toxicity. Glucocorticoids increase the risk for pregnancy-induced hypertension and diabetes.

KEY POINTS

- Women with chronic kidney disease (CKD) have a greater risk for preeclampsia, acute kidney injury, progression of CKD, end-stage kidney disease, preterm delivery, gestational hypertension, intrauterine growth retardation, and fetal loss.
- Kidney transplant recipients should wait at least 1 to 2 years after transplantation with a stable allograft and stable immunosuppression before attempting conception.
- Mycophenolate mofetil and sirolimus used in kidney transplant recipients are teratogenic and must be discontinued before attempting conception.

Chronic Kidney Disease

Definition and Staging

Chronic kidney disease (CKD) is defined as abnormal kidney structure or function present for >3 months. CKD is stratified into stages 1 to 5 based on the level of estimated glomerular filtration rate (eGFR). Stage G1 does not have a reduction in eGFR and therefore is defined by the presence of anatomical defects or markers of kidney damage such as albuminuria, hematuria, or electrolyte abnormalities. Because albuminuria is associated with increased renal and cardiovascular morbidity and mortality, the Kidney Disease: Improving Global Outcomes (KDIGO) group further subdivides the eGFR-based kidney stages by degree of albuminuria (**Figure 21**). This dual eGFR and albuminuria staging algorithm provides a means for predicting which patients are at highest risk for progression of CKD to end-stage kidney disease (ESKD), defined as CKD stage G5 treated with chronic dialysis or kidney transplantation.

Epidemiology and Pathophysiology

CKD affects approximately 15% of the U.S. adult population. About 50% of patients with prevalent CKD have stage G3 disease or worse. The prevalence of CKD has remained stable in the United States, with the highest prevalence seen in patients aged ≥60 years. Patients with lower eGFR are more likely to have higher degrees of albuminuria. Advanced CKD, defined by stages G4 or G5, is present in <1% of the population. Compared with men, women have a higher prevalence of both eGFR <60 mL/min/1.73 m^2 (7.6% versus 6.1%) and albuminuria (11.2% versus 8.9%).

GFR categories (mL/min/1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g	30-300 mg/g	>300 mg/g
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

FIGURE 21. The Kidney Disease: Improving Global Outcomes (KDIGO) chronic kidney disease staging system. Prognosis of chronic kidney disease by glomerular filtration rate and albuminuria category. CKD = chronic kidney disease; GFR = glomerular filtration rate.

Reprinted with permission from KDIGO: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1-150. Copyright 2013.

CKD results from various etiologies that cause chronic damage to the glomeruli, tubulointerstitium, or vasculature. Glomerular damage is reflected by albuminuria. Tubulointerstitial damage may manifest as abnormalities in renal-concentrating abilities and low-grade tubular proteinuria. As the underlying structural abnormalities progress, GFR falls below normal levels.

Most patients with CKD do not progress to ESKD. In healthy adults aged >30 years, the average rate of decline of eGFR is approximately 1 mL/min/1.73 m^2 per year; those with risk factors such as increased albuminuria/proteinuria and/or diabetic kidney disease are likely to have more rapid progression. The most important predictors of progression to ESKD are baseline eGFR and severity of albuminuria/proteinuria. The eGFR trajectory over time adds prognostic value for ESKD and cardiovascular outcomes. Renal risk variants in the apolipoprotein L1 (*APOL1*) gene are prevalent in people with West African ancestry and are associated with higher rates of ESKD and progression of CKD, regardless of diabetes mellitus status (see Genetic Disorders and Kidney Disease).

Screening

Controversy exists regarding routine screening of asymptomatic patients for CKD. Screening patients at risk for CKD, including those with diabetes, hypertension, or a family history of kidney disease, is generally recommended.

Clinical Manifestations

CKD is typically asymptomatic except in advanced stages (G4, G5). As eGFR falls below 60 mL/min/1.73 m^2, numerous alterations in metabolic pathways, including 1,25-dihydroxyvitamin D production and erythrocyte production, become altered due to the loss of nephron mass and hormone synthesis. Moderate to severe CKD can also result in impaired ability to excrete salt and water, manifesting as edema. Patients with nephrotic-range proteinuria may also develop edema or anasarca.

When CKD progresses to ESKD, uremic symptoms, such as fatigue, nausea, loss of appetite, insomnia, irritability, difficulty concentrating, confusion, or pruritus can occur. Uremia can also induce pleuritis and pericarditis. Crystalized cutaneous urea and other nitrogenous waste deposits appear as chalky skin deposits, termed uremic frost, and occur rarely as a late manifestation of uremia (**Figure 22**). A large proportion of patients with CKD stage G5 manifest few or only intermittent uremic symptoms.

Diagnosis

eGFR can be established using serum creatinine and the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration creatinine equation. If confirmation of GFR is required because of conditions that affect serum creatinine

FIGURE 22. Uremic frost presenting as powdery deposits of urea and uric acid salts on the skin in a patient with untreated chronic kidney disease. Uremic frost is a late and rarely seen manifestation of uremia.

independent of GFR (such as extremes of muscle mass or diet), cystatin C should be measured to employ the CKD-EPI cystatin C or creatinine-cystatin C equation. Initial assessment of albuminuria includes a spot urine albumin-creatinine ratio. If confirmation of albuminuria is required, the albumin excretion rate should be measured from a timed urine collection. See Clinical Evaluation of Kidney Function for more information.

Diagnosis of CKD requires an eGFR <60 mL/min/1.73 m^2 confirmed at least 3 months after initial assessment, or persistent proteinuria or albuminuria regardless of eGFR. Kidney biopsy is used to determine the etiology of CKD when a glomerular or tubulointerstitial disease is likely and when specific therapy is available to delay or prevent further kidney injury. Kidney biopsy is not routinely performed in the presence of shrunken kidneys (<9 cm), which generally indicate chronic irreversible disease. Ultrasound findings of hyperechoic kidneys may be noted consistent with medical kidney disease and usually reflect long-standing CKD. There is currently a lack of evidence regarding the use of urinalysis as a routine screening test for CKD.

Patients who experience acute kidney injury (AKI) can have slow recovery; studies have demonstrated that kidney function can continue to improve for up to 1 year after an initial episode of AKI. Therefore, although diagnosis of CKD requires at least 3 months of persisting abnormalities in structure or function, a diagnosis of CKD made 3 months after AKI may be premature. AKI is a risk factor for subsequent CKD. Both the severity of AKI and the time required for recovery

from AKI influence the likelihood of having CKD after 1 year. Thirty percent to 47% of patients have CKD 1 year after an episode of AKI, and 1% to 3% of patients progress to stage G5 or ESKD. Therefore, patients with a history of AKI should have their kidney function monitored.

KEY POINTS

- Chronic kidney disease is defined as abnormal kidney structure or function present for >3 months.
- Staging of chronic kidney disease is based on estimated glomerular filtration rate and albuminuria.
- Acute kidney injury is a substantial risk factor for subsequent chronic kidney disease.

Complications and Management

According to KDIGO guidelines, referral to a nephrologist is indicated for evaluation and management of CKD in the presence of the following: AKI or an abrupt, sustained fall in GFR; GFR <30 mL/min/1.73 m^2; persistent albuminuria (>300 mg/g); progression of CKD; erythrocyte casts; >20 erythrocytes/hpf that is sustained and not readily explained; hypertension refractory to treatment with four or more antihypertensive agents; persistent abnormalities of serum potassium; recurrent or extensive nephrolithiasis; or hereditary kidney disease.

A kidney failure risk equation (KFRE) has been developed and validated (https://kidneyfailurerisk.com). The KFRE uses four variables (age, sex, eGFR, and albuminuria) to predict 2-year and 5-year risk for ESKD in patients with CKD stages G3 to G5. The KFRE performs well across age, sex, and presence/absence of diabetes. The use of this equation is consistent with KDIGO guidelines, which recommend integration of risk prediction in the evaluation and management of CKD.

Cardiovascular Disease

Cardiovascular disease is the leading cause of death among patients with CKD. The risk for cardiovascular-related death in patients with CKD stages G3 and G4 is four to five times higher than the risk for progression to ESKD. Mortality risk increases with decreasing eGFR and increasing albuminuria. Unfortunately, many clinical trials guiding the prevention or treatment of cardiovascular disease did not include patients with advanced CKD. However, most post hoc analyses of randomized controlled trials that had participants with some degree of CKD demonstrated efficacy regardless of baseline CKD status, including interventions such as percutaneous coronary interventions. Thus, experts recommend against withholding otherwise efficacious therapies from those with CKD due to unsubstantiated concerns of lack of efficacy or harm.

Hypertension

Both KDIGO and the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) blood pressure guideline recommend a target blood pressure of <130/80 mm Hg in patients with hypertension and CKD.

An ACE inhibitor or an angiotensin receptor blocker is a preferred drug for treatment of hypertension for patients with stage G3 CKD or higher or for those with stage G1 or G2 CKD with albuminuria (albumin-creatinine ratio ≥300 mg/g). These medications may slow the progression of CKD in some patients. Thiazide diuretics are a cornerstone of hypertension treatment but lose efficacy with severe CKD. Therefore, loop diuretics serve an important role in managing salt and water retention associated with proteinuria and CKD. Dietary sodium chloride restriction is essential for blood pressure control in most forms of CKD. KDIGO recommends restricting sodium intake to <2000 mg/d.

See Hypertension for more information.

Dyslipidemia

Elevated LDL cholesterol and triglyceride levels with low HDL cholesterol levels are common among patients with CKD. Conflicting data exist on the effect of treating dyslipidemia in reducing proteinuria and in slowing the progression of CKD. Statins have been shown to reduce cardiovascular and all-cause mortality in patients with CKD, although large trials have failed to demonstrate a mortality benefit for statins in patients with dialysis-dependent ESKD. KDIGO guidelines recommend treatment with a statin in all patients aged ≥50 years with non-dialysis-dependent CKD and in adults aged 18 to 49 years with non-dialysis-dependent CKD and any one of the following: coronary artery disease, diabetes, prior ischemic stroke, or a >10% estimated risk for coronary death or nonfatal myocardial infarction. Statins are also recommended for adult kidney transplant recipients. The 2018 AHA/ACC Guideline on the Management of Blood Cholesterol indicates that it is reasonable to initiate a moderate-intensity statin with or without ezetimibe in adults 40 to 75 years of age with CKD, an LDL cholesterol measure of 70 to 189 mg/dL (1.8 to 4.9 mmol/L), and a 10-year atherosclerotic cardiovascular disease risk of ≥7.5%. The guideline recommends against initiating statin therapy in patients on dialysis, but it may be reasonable to continue statins in patients beginning dialysis therapy.

Dyslipidemia associated with the nephrotic syndrome helps maintain plasma oncotic pressure but, over time, may hasten the progression of glomerular injury. Dyslipidemia in the nephrotic syndrome requires aggressive treatment to prevent atherosclerotic disease. See Glomerular Diseases for more information on the nephrotic syndrome.

Coronary Artery Disease

Coronary artery disease (CAD) prevalence is significantly increased among patients with CKD compared with the general population. This is partly explained by the high prevalence of shared risk factors/comorbidities such as diabetes or hypertension. However, CKD is independently associated with CAD. This association strengthens with declining eGFR and rising albuminuria.

In patients with CKD, serum biomarkers for myocardial ischemia such as cardiac troponins may be chronically elevated due to decreased renal clearance. Serial troponin measurements and other markers such as creatine kinase-MB can help distinguish acute ischemia from chronic elevations.

KEY POINTS

- Guidelines recommend a target blood pressure of <130/80 mm Hg in patients with hypertension and chronic kidney disease.
- Treatment of hypertension in patients with stage G3 chronic kidney disease (CKD) or higher or for those with proteinuric CKD (albumin-creatinine ratio ≥300 mg/g) includes an ACE inhibitor or angiotensin receptor blocker, dietary sodium restriction to <2000 mg/d, and addition of a diuretic as needed to control vascular volume.
- The Kidney Disease: Improving Global Outcomes guidelines recommend treatment with a statin in all patients with non-dialysis-dependent chronic kidney disease (CKD) who are older than 50 years of age and in adults 18 to 49 years of age with non-dialysis-dependent CKD and any one of the following: coronary artery disease, diabetes mellitus, prior ischemic stroke, or a >10% estimated risk for coronary death or nonfatal myocardial infarction.
- The 2018 American Heart Association/American College of Cardiology Guideline on the Management of Blood Cholesterol indicates that it is reasonable to initiate a moderate-intensity statin with or without ezetimibe in adults 40 to 75 years of age with chronic kidney disease, an LDL cholesterol measure of 70 to 189 mg/dL (1.8 to 4.9 mmol/L), and a 10-year atherosclerotic cardiovascular disease risk of ≥7.5%.

Chronic Kidney Disease-Mineral and Bone Disorder

As kidney function declines, homeostasis of calcium and phosphorus becomes compromised, resulting in alterations of blood levels of calcium, phosphorus, regulatory hormones, bone mineralization, and pathologic calcification. The term *chronic kidney disease-mineral and bone disorder* (CKD-MBD) encompasses these changes.

Calcium and Phosphorus Homeostasis

Three hormones are largely responsible for regulating calcium and phosphorus homeostasis: parathyroid hormone (PTH), vitamin D, and fibroblast growth factor 23 (FGF-23). PTH is the most important regulator of calcium and phosphorus concentrations. PTH has three separate mechanisms to increase serum calcium: stimulation of osteoclasts to resorb bone, hydroxylation of 25-hydroxyvitamin D in the kidneys, and tubular reabsorption of calcium (**Figure 23**). Concurrently, PTH induces renal phosphorus excretion.

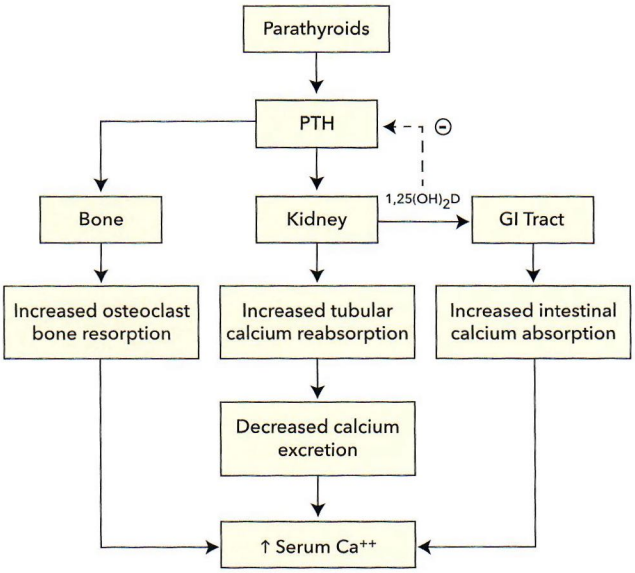


FIGURE 23. Overview of the metabolic systems that maintain calcium homeostasis. Parathyroid hormone (PTH) stimulates increased 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] synthesis by the kidneys, and 1,25$(OH)_2$D causes feedback suppression of PTH production.

Ca^{++} = ionized calcium; GI = gastrointestinal; 1,25$(OH)_2$D = 1,25-dihydroxyvitamin D (calcitriol); PTH = parathyroid hormone; ↑ = increased.

FGF-23 is a peptide secreted by osteocytes and likely by other types of bone cells. It acts on the kidney to induce phosphaturia and downregulates 1α-hydroxylase to inhibit synthesis of 1,25-dihydroxyvitamin D. FGF-23 rises in stage G3a CKD, preceding PTH elevation. As GFR falls and PTH rises, PTH directly stimulates further FGF-23 production by osteocytes. Initially, the high FGF-23 serves to increase renal phosphorus excretion and helps maintain normal phosphorus levels as GFR declines.

As CKD progresses, increased FGF-23 and decreased nephron mass reduce the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by renal tubular cells. Reduction in 1,25-dihydroxyvitamin D levels results in lower intestinal absorption of calcium and phosphorus in the gut, mitigating increases in serum phosphorus but also contributing to hypocalcemia, especially late in CKD. Reduced 1,25-dihydroxyvitamin D levels also increase PTH production by the parathyroid glands, and hypocalcemia is a potent stimulus for further increases in PTH levels.

Increased plasma PTH caused by CKD is referred to as *secondary hyperparathyroidism*. Increased PTH levels result in reduced calcium excretion, increased calcium absorption from the gut, increased phosphorus excretion by the kidneys, and activation of osteoclast bone resorption. Early in CKD, the increase in renal phosphorus excretion induced by PTH and FGF-23 enables normal phosphorus levels despite reduced renal excretory capacity. However, as CKD progresses, compensation for the increased release of phosphorus from bone is lost, and phosphorus levels rise. This results in a vicious cycle as hyperphosphatemia stimulates PTH production.

If secondary hyperparathyroidism cannot be adequately controlled, tertiary hyperparathyroidism can ensue. Tertiary hyperparathyroidism is the result of prolonged PTH stimulation needed to maintain eucalcemia. This prolonged stimulation results in severe parathyroid hyperplasia with elevated PTH levels that are no longer suppressible by elevated plasma calcium concentration.

Laboratory Abnormalities

Serum calcium and phosphorus levels typically remain in the normal range until the eGFR drops below 30 mL/min/1.73 m^2, at which point the ability of elevated FGF-23 and PTH levels to promote phosphorus excretion becomes overwhelmed, and hyperphosphatemia develops. Progressive decline in 1,25-dihydroxyvitamin D levels results in reduced intestinal calcium absorption, and hyperphosphatemia promotes precipitation of calcium and phosphorus in extraskeletal tissues, leading to hypocalcemia.

In addition to reduced conversion of 25-hydroxyvitamin D (calcidiol) to 1,25-dihydroxyvitamin D (calcitriol), patients with CKD also have a higher prevalence of 25-hydroxyvitamin D deficiency. KDIGO guidelines recommend that patients with an eGFR <60 mL/min/1.73 m^2 be evaluated for 25-hydroxyvitamin D deficiency and supplemented as per guidelines for the general population.

PTH levels are often elevated in patients with an eGFR <60 mL/min/1.73 m^2 and progressively increase with worsening CKD. KDIGO guidelines recommend measuring intact PTH levels to aid in the detection and management of secondary hyperparathyroidism and its complications (**Table 32**).

Vascular Calcification

An increased prevalence of arterial calcification, including the coronary arteries, has been noted in patients with CKD (**Figure 24**); the burden of calcification is highest in patients with ESKD. Arterial calcification reduces vascular compliance and contributes to the increased prevalence of left ventricular hypertrophy observed in patients with CKD. Arterial calcification is associated with cardiovascular and all-cause mortality; KDIGO guidelines suggest treating patients with CKD and arterial calcification as appropriate for patients in the highest category of cardiovascular risk, although treatments specifically targeted at reducing vascular calcification have not been shown to improve clinical outcomes.

TABLE 32. Laboratory Abnormalities in Hyperparathyroidism

	Types of Hyperparathyroidism		
	Primary	**Secondary**	**Tertiary**
Calcium	High	Low	High
Phosphate	Low to low normal	High	High
PTH	High	High	Very high
Calcitriol	High	Low	Low
FGF-23	Normal to slightly elevated[a]	High	High

Calcitriol = 1,25-dihydroxyvitamin D; FGF-23 = fibroblast growth factor 23; PTH = parathyroid hormone.

[a]Data vary.

FIGURE 24. Calcified vessels in a patient with chronic kidney disease.

Renal Osteodystrophy

Renal osteodystrophy refers to alteration of bone morphology with CKD, rendering affected patients at increased risk for bone pain, falls, and fractures. Five main types of histologic changes in bone can occur (discussed below). Diagnosis of renal osteodystrophy can be supported by PTH levels followed over time, but definitive diagnosis requires a bone biopsy. KDIGO guidelines recommend a bone biopsy if knowledge of the type of renal osteodystrophy will affect treatment decisions.

Osteitis Fibrosa Cystica

Osteitis fibrosa cystica is due to abnormally high bone turnover that occurs after prolonged exposure of bone to sustained high levels of PTH in secondary hyperparathyroidism. It is associated with increased number and activity of osteoblasts and osteoclasts and expansion of osteoid surfaces. Classic skeletal changes on radiograph include subperiosteal resorption of bone, most prominently at the phalanges of the hands, and radiolucent bone cysts of the long bones (**Figure 25**).

Adynamic Bone Disease

Adynamic bone disease occurs when there is a lack of bone cell activity and a markedly reduced rate of bone turnover. Histopathologic abnormalities include decreased osteoclast activity with decreased osteoid. Patients have suppressed PTH levels (due to chronic illness or aggressive treatment with vitamin D analogues) or skeletal resistance to PTH from down-regulation of the bone PTH receptor due to high circulating PTH levels. Adynamic bone disease should be excluded before initiation of bisphosphonate therapy because these drugs can cause and/or worsen the disease by inhibiting osteoclast activity.

FIGURE 25. Humerus showing radiologic changes of osteitis fibrosa cystica, characterized by bone cysts and radiolucent lytic areas of the long bones caused by brown tumors. Brown tumors represent a collection of osteoclasts and fibrous material that appears brown secondary to hemosiderin deposition.

Osteomalacia

Osteomalacia is characterized by decreased mineralization of osteoid at sites of bone turnover. Although patients with CKD are at increased risk for osteomalacia, CKD does not cause osteomalacia per se; vitamin D deficiency caused by coexisting factors such as intestinal malabsorption or restricted access to sunlight are often present.

Mixed Uremic Osteodystrophy

Mixed uremic osteodystrophy is the term used to describe renal osteodystrophy containing elements of both high bone turnover and decreased mineralization.

Osteoporosis

Patients with CKD may also develop osteoporosis. KDIGO guidelines indicate that in patients with CKD stages G3a to G5 with evidence of CKD-MBD and/or risk factors for osteoporosis, bone mineral density testing is suggested to assess fracture risk if results will affect treatment decisions. Patients with CKD who have osteoporosis and eGFR >30 mL/min/1.73 m^2 can be treated as per the non-CKD population. Bisphosphonates are not recommended for use in patients with eGFR <30 to 35 mL/min/1.73 m^2. However, for patients with CKD stage G4 to G5 with fragility fractures and suspected osteoporosis, treatment may be considered, usually in conjunction with an expert in CKD-MBD.

Management

Elevated phosphorus, PTH, and FGF-23 levels are associated with risk for adverse cardiovascular events and mortality among patients with CKD and ESKD. Observational studies suggest a mortality benefit of therapy with phosphate binders and vitamin D analogues to lower serum phosphorus and PTH. Unfortunately, prospective randomized trials are lacking in this field. Some trials comparing noncalcium-based to calcium-based binders suggest a mortality benefit of noncalcium-based agents. A randomized trial of calcimimetics, which inhibit PTH secretion via activation of the calcium-sensing receptor, did not show benefit in the composite outcome of cardiovascular events and mortality. However, secondary analysis of available data suggests benefit for both the composite outcome and reduction in need for parathyroidectomy as well as fewer cases of calciphylaxis. Oral and intravenous calcimimetics are available in the United States. There are currently no therapies aimed at lowering FGF-23 levels.

KDIGO guidelines for treatment of CKD-MBD are based on the available data and expert opinion (**Table 33**). In patients with CKD stages G3a to G5, treatment is based on serial assessments of phosphorus, calcium, and PTH levels. KDIGO guidelines recommend that elevated phosphorus levels be lowered toward the normal range. Treatment options include dietary modifications and administration of phosphate binders. For patients with CKD stages G3a to G5 who are not on dialysis, optimal PTH levels are not known. Patients with rising or elevated levels should be evaluated for potentially modifiable contributors, including elevated phosphorus levels or vitamin D deficiency.

KDIGO guidelines recommend avoiding hypercalcemia and inappropriate calcium loading given concerns that exposure to exogenous calcium contributes to harmful vascular calcification in all stages of CKD. Use of calcitriol and vitamin D analogues to lower PTH levels in patients with CKD stages G3a to G5 who are not on dialysis should be avoided. Instead, these agents should be reserved for patients with CKD stages G4 to G5 with severe and progressive hyperparathyroidism. The dose of calcium-based phosphate binders should be minimized, or noncalcium-based binders can be used preferentially.

In patients on dialysis, KDIGO guidelines recommend use of calcimimetics, calcitriol, or vitamin D analogues, or a combination of calcimimetics and calcitriol or vitamin D analogues, to lower PTH levels.

Tertiary hyperparathyroidism does not respond to phosphate binders or calcitriol therapy. Patients often require parathyroidectomy for definitive treatment.

KEY POINTS

- Chronic kidney disease-mineral and bone disorder is characterized by alterations of blood levels of the calcium, phosphorus, and regulatory hormones; bone mineralization; and pathologic calcification.
- Management of chronic kidney disease-mineral and bone disorder focuses upon normalizing serum phosphorus, avoiding hypercalcemia, and addressing modifiable factors.

(Continued)

TABLE 33. Medications Used in the Treatment of Chronic Kidney Disease-Mineral and Bone Disorder

Class/Agent	Mechanism of Action
Phosphate binders	Binds phosphate in GI tract before it can be absorbed; the binder-phosphate complex is excreted in the stool.
Noncalcium-based binders (e.g., sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate)[a]	
Iron-based (noncalcium) binders (e.g., sucroferric oxyhydroxide, ferric citrate)[a]	
Calcium-based binders (e.g., calcium carbonate, calcium acetate)	
Aluminum-based binders (e.g., aluminum hydroxide)[b]	
Activated vitamin D agents (e.g., calcitriol, paricalcitol, doxercalciferol)	Inhibits PTH secretion via binding the vitamin D receptor on the parathyroid gland.
Calcimimetic agents (e.g., cinacalcet, etelcalcetide)	Inhibits PTH secretion via binding the calcium-sensing receptor, resulting in a morphology change and rendering the receptor more sensitive to the presence of calcium; for a given level of calcium, there is greater inhibition of PTH secretion.

Calcitriol = 1,25-dihydroxyvitamin D; GI = gastrointestinal; PTH = parathyroid hormone.

[a]Preferred over calcium-based binders.

[b]Aluminum-based phosphate binders are associated with aluminum toxicity and should no longer be used in patients with chronic kidney disease.

KEY POINTS *(continued)*

HVC

- Use of calcitriol and vitamin D analogues to lower parathyroid hormone should be avoided in patients with chronic kidney disease who are not on dialysis unless they have progressive hyperparathyroidism.
- Noncalcium-based phosphate binders should be used preferentially over calcium-based options in patients with chronic kidney disease-mineral and bone disorder.

Anemia

Anemia in the setting of CKD is common, and its prevalence increases as CKD progresses into stages G4 and G5. Most often normocytic, anemia in CKD is multifactorial with contributing factors, including the relative lack of erythropoietin production due to decline in functional renal mass; erythropoietin resistance; disordered iron handling with elevated hepcidin leading to functional iron deficiency as well as true iron deficiency with blood loss; and neocytolysis in the uremic milieu.

Concern for the development of left ventricular hypertrophy and observational data linking higher hemoglobin levels with better outcomes led to the belief that higher hemoglobin values were beneficial in patients with CKD and ESKD. However, several large randomized controlled trials demonstrated either no benefit or an increased risk for cardiovascular events and strokes in groups randomly assigned to higher hemoglobin targets via erythropoiesis-stimulating agents (ESAs). Furthermore, these trials revealed only modest improvements in fatigue and no benefit in physical functioning with higher hemoglobin targets. Thus, current KDIGO recommendations as well as American Society of Nephrology (ASN) high-value care tenets suggest considering ESAs only for patients with CKD who have hemoglobin concentrations <10 g/dL (100 g/L).

An FDA boxed warning for use of ESAs includes an increased risk for thromboembolic events in postsurgical patients not receiving anticoagulant therapy, and an increased risk for serious cardiovascular events when ESAs are administered to patients with hemoglobin levels >11 g/dL (110 g/L).

Prolyl hydroxylase inhibitors are a novel class of drugs under investigation to treat anemia associated with CKD. These oral medications can increase the endogenous production of erythropoietin and reduce hepcidin levels, improving iron availability and increasing hemoglobin levels.

All patients with CKD and anemia should have iron profiles assessed, including total iron-binding capacity and ferritin levels. KDIGO suggests maintaining transferrin saturation levels >30% and serum ferritin levels >500 ng/mL (500 µg/L) using either oral or intravenous iron supplementation. Inadequate iron stores contribute to ESA hyporesponsiveness. Blood transfusions can be used in patients with severe anemia or symptoms; however, erythrocyte transfusions should be minimized because of concerns for iron overload and sensitization to HLA antigens, which may lead to allosensitization and increased waiting times for kidney transplantation.

Metabolic Acidosis

Metabolic acidosis frequently occurs in patients with CKD because of defective acid excretion. Untreated metabolic acidosis can lead to muscle loss (due to increased muscle proteolysis) and bone loss (due to increased bone resorption and impaired bone formation). Patients with early CKD have a normal anion gap hyperchloremic metabolic acidosis due to impaired ammoniagenesis, resulting in reduced bicarbonate generation. As GFR declines, organic and inorganic anions are retained, and an increased anion gap metabolic acidosis develops.

Large observational studies have shown a strong association between lower serum bicarbonate levels and increased progression of CKD and mortality. Meta-analysis of randomized trials of alkali therapy, most commonly sodium bicarbonate or sodium citrate, support delayed progression of CKD. KDIGO guidelines recommend initiating alkali therapy when the serum bicarbonate level is chronically <22 mEq/L (22 mmol/L). The alkali salt therapy dose should be titrated to achieve a serum bicarbonate level within the normal range; excessive alkali therapy in the setting of a reduced GFR may induce a metabolic alkalosis, which is associated with increased mortality. An alternative approach is the provision of alkali through a diet rich in fruits and vegetables, which may have equal efficacy in improving serum bicarbonate levels.

Nephrotoxins

Two major issues exist regarding drug administration in patients with CKD: 1) Renally excreted drugs require dose adjustment to avoid accumulation and potential side effects; and 2) Reduced functional nephron mass increases the probability that a potentially nephrotoxic drug will cause nephrotoxicity. Nephrotoxins may cause AKI or CKD.

Conceptually, it is useful to compartmentalize nephrotoxic medications by their main site of action. Several medications, including NSAIDs, calcineurin inhibitors, and ACE inhibitors/angiotensin receptor blockers, have effects on glomerular blood flow. Patients with AKI who are on NSAIDs should have the medications immediately discontinued. For patients with CKD, the ASN recommends the avoidance of NSAIDs, including cyclooxygenase-2 inhibitors, due to the risk of worsening kidney function. ACE inhibitors or angiotensin receptor blockers are a cornerstone of treatment for patients with CKD; however, during episodes of acute illness and/or volume depletion, these drugs increase the risk for AKI due to their effects on intraglomerular pressure. Drugs that cause glomerular injury, tubular injury, or tubulointerstitial nephritis are reviewed in Acute Kidney Injury.

Medications or toxin exposures associated with the development and progression of CKD include proton pump inhibitors, NSAIDs, combination ingredient analgesics, lithium, exposure to lead, and environmental exposure to the carcinogenic plant toxin aristolochic acid. Care for patients with CKD should include avoidance of medications such as NSAIDs and proton pump inhibitors as well as dose adjustment of frequently used medications, including antibiotics and direct oral anticoagulants.

Proteinuria

The severity of proteinuria is strongly associated with adverse clinical outcomes, including progression of CKD to ESKD, cardiovascular morbidity, and mortality. It is unclear whether proteinuria is a marker of the underlying severity of kidney damage and disease, or if proteinuria itself activates inflammatory pathways and contributes to tubulointerstitial fibrosis. Although renin-angiotensin system blockade will decrease proteinuria, the use of dual therapy combining ACE inhibitors, angiotensin receptor blockers, or direct renin inhibitors results in more adverse events (hyperkalemia, hypotension, AKI) without additional cardiovascular or renal benefits.

Interventions to Slow Renal Decline

Protein Restriction

In animal models, protein-restricted diets slow the progression of kidney disease by reducing glomerular filtration pressure. However, in the Modification of Diet in Renal Disease study, no definitive benefit was seen in renal outcomes in patients randomly assigned to the low-protein (0.6 g/kg/d) group. Although there is insufficient evidence to recommend routine use of low-protein diets to slow progression of CKD, high-protein diets may accelerate symptoms of uremia in patients with stage G5 CKD. Small studies suggest that low-protein diets might delay the onset of symptomatic uremia and the need for renal replacement therapy in patients with stage G5 CKD not yet on dialysis.

Smoking Cessation

Data strongly support the adverse impact of tobacco exposure on renal function. No prospective studies have been done to demonstrate improvement in CKD with tobacco cessation. However, given the well-documented harms of tobacco exposure and the benefits gained with cessation in other organ systems, smoking cessation should be encouraged and supported for patients with CKD as well.

Diabetes Management

In patients with type 2 diabetes and CKD, the American Diabetes Association (ADA) and KDIGO recommend the addition of a sodium-glucose cotransporter 2 (SGLT2) inhibitor to metformin to reduce the risk of CKD progression and cardiovascular events. The ADA recommends the use of a glucagon-like peptide 1 (GLP-1) receptor agonist in patients with CKD who are at risk for cardiovascular events to reduce risk of progression of albuminuria and cardiovascular events. KDIGO recommends the adding a GLP-1 receptor agonist in patients who have not achieved individualized glycemic targets despite use of metformin and SGLT2 inhibitors, or who are unable to use those medications. Neither metformin nor SGLT2 inhibitors are recommended in patients with an eGFR <30 mL/min/1.73 m^2. See Glomerular Diseases for more information on diabetic kidney disease, diabetes mellitus, and SGLT2 inhibitors.

KEY POINTS

HVC
- Erythropoiesis-stimulating agents should not be used for most patients with chronic kidney disease and hemoglobin >11 g/dL (110 g/L) because of an increased risk for serious cardiovascular events and strokes.
- The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment of metabolic acidosis with alkali therapy in patients with chronic kidney disease when the serum bicarbonate is chronically <22 mEq/L (22 mmol/L).
- Routine care for patients with chronic kidney disease should include avoidance of medications such as NSAIDs and proton pump inhibitors as well as dose adjustment of frequently used medications, including antibiotics and direct oral anticoagulants.

HVC
- ACE inhibitors and angiotensin receptor blockers decrease proteinuria and slow progression of proteinuric kidney diseases, but use of both drug classes in combination results in more adverse events without additional cardiovascular or renal benefits.
- Sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists should be considered for patients with type 2 diabetes mellitus and chronic kidney disease independent of hemoglobin A_{1c}.

Special Considerations

Imaging Contrast Agents

Intravenous iodinated contrast has long been associated with AKI (termed contrast-associated nephropathy [CAN]). Contrast-induced nephropathy (CIN), a subset of CAN, is directly mediated by the contrast agent. Recent data suggest that the frequency of CIN is less than originally believed, as hospitalized patients who require noncontrast imaging develop AKI at the same frequency. However, the risk for CAN and CIN increases with increasing severity of CKD. The 2018 American College of Radiology (ACR) Manual on Contrast Media suggests avoidance of iodinated contrast for patients with an eGFR <30 mL/min/1.73 m^2. Patients with CKD and an eGFR <30 mL/min/1.73 m^2 who require iodinated contrast should receive intravenous hydration with isotonic saline before and after receiving contrast unless there is evidence of frank pulmonary edema. Prophylactic saline infusion should also be considered in patients with an eGFR of 30 to 44 mL/min/1.73 m^2 who have other risk factors for AKI. See Acute Kidney Injury for more information on CIN.

Group I gadolinium-based contrast media (GBCM) used in MRI have been associated with nephrogenic systemic fibrosis (NSF) in patients with ESKD on dialysis and advanced CKD or AKI with eGFR <30 mL/min/1.73 m^2. These patients present with symmetrical, fibrotic indurated papules, plaques, or subcutaneous nodules most commonly located on the legs, the mid-thighs, and upper arms (**Figure 26**). The ACR and the National Kidney Foundation consider group II GBCM to present a very low to nonexistent risk of NSF and should be the GBCM type used for patients at risk for NSF who must receive MRI with contrast. There is insufficient data to quantify risk in patients receiving group III GBCM. Additional recommendations include using the lowest volume of contrast adequate for the study and scheduling the study temporally close to the next hemodialysis session for those receiving hemodialysis.

FIGURE 26. Indurated papules and plaques are characteristic of early nephrogenic systemic fibrosis. These will eventually coalesce into large plaques.

Vaccination

Patients with CKD are at increased risk for infections that can be prevented by vaccination; however, these patients also have impaired immune responses to vaccines. Patients with CKD should receive vaccinations according to CDC guidelines, including COVID-19, which state that vaccinations in patients with CKD may be more effective when performed before the need for chronic dialysis or kidney transplantation. Special considerations for patients with CKD include the following:

- Patients with advanced CKD near dialysis dependence or those with ESKD on hemodialysis not already immune to hepatitis B virus (HBV) should be vaccinated against HBV.
- Patients with CKD or the nephrotic syndrome should receive the 13- and 23-valent pneumococcal vaccines, with revaccination with the 23-valent vaccine after a minimum of 5 years.
- Influenza vaccine should be administered annually to patients with CKD; patients with ESKD should preferentially receive the inactivated influenza vaccine.

Vascular Access

Patients with advanced CKD may ultimately require renal replacement therapy (RRT). For patients who choose hemodialysis, timely vascular access creation is essential. Referral to an experienced surgeon many months before dialysis is critical because arteriovenous fistula placement, the safest and most enduring option for vascular access, can be technically challenging and may require several months for full maturation. Arteriovenous fistulas have superior clinical outcomes compared with arteriovenous grafts. Tunneled catheters may be used for dialysis promptly after placement, but they are associated with increased risk for bloodstream infection and death.

Protecting the nondominant arm veins is paramount and involves limiting phlebotomy and intravenous catheters in that arm. Data demonstrate that peripherally inserted central catheters (PICC lines) placed before or after initiation of hemodialysis are independently associated with a 15% to 20% lower likelihood of transition to any working fistula or graft. The ASN recommends that PICC line catheters should be avoided in patients with an eGFR <60 mL/min/1.73 m^2. Avoidance of subclavian venous catheters helps limit subclavian stenosis, which can impair the proper functioning of an arteriovenous access used for dialysis.

Older Patients

CKD stages G1 through G3a in older patients without albuminuria is of minimal clinical importance. For older patients with progressing or severe CKD necessitating discussions about RRT and/or referral for evaluation for kidney transplantation, a patient-centered approach is preferred. Comorbid medical conditions, functional status, expected outcomes, and patient preferences regarding goals of care should be considered. For patients aged ≥80 years at the start of hemodialysis treatment, data demonstrate better survival among those who received pre-hemodialysis nephrology care that followed a planned management pathway, had good nutritional status, and had an arteriovenous fistula as vascular access for hemodialysis at the time of hemodialysis initiation.

KEY POINTS

- Patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2, who require iodinated contrast should receive intravenous hydration with isotonic saline before and after receiving contrast unless there is evidence of frank pulmonary edema.
- For patients with advanced chronic kidney disease who require MRI with a gadolinium-based contrast media (GBCM), risk for nephrogenic systemic fibrosis is reduced by using a group II GBCM at the lowest volume of contrast possible and timing proximate to the next scheduled hemodialysis for dialysis-dependent patients.
- In patients with chronic kidney disease, peripherally inserted central venous catheters and subclavian venous catheters should be avoided to maintain central vein patency for future dialysis vascular access.
- Patients with advanced chronic kidney disease who choose hemodialysis for renal replacement therapy should be referred to an experienced surgeon for arteriovenous fistula placement months before the anticipated need for dialysis.

End-Stage Kidney Disease

CKD stage G5 is defined as an eGFR <15 mL/min/1.73 m^2, and ESKD is defined as CKD stage G5 treated with chronic dialysis or kidney transplantation. About 10% of patients with CKD stage G3 progress to ESKD, but most die from cardiovascular disease or infection before they progress to advanced CKD.

Patients with an eGFR <30 mL/min/1.73 m^2 should be educated about RRT treatment options, including hemodialysis, peritoneal dialysis, and kidney transplantation. Studies demonstrate no benefit in starting RRT in asymptomatic patients or at a specific eGFR cutoff compared with watchful waiting and initiating RRT for symptoms or metabolic abnormalities that are refractory to medical treatment. Patients with advanced age or multiple comorbidities may not want any of these life-sustaining options. There has been increasing use of "kidney supportive care," which involves services aimed at improving the quality of life for patients with advanced CKD. Treatment is aligned with the patient's goals through culturally sensitive shared decision-making and advance care planning, along with treating symptoms resulting from uremia, hypervolemia, hyperkalemia, and/or acidosis. Care should align with patient preferences and maximize the patient's quality of life (**Table 34**). Shared decision-making regarding goals of care for patients with advanced CKD is an important high-value care tenet of the ASN.

Dialysis

Hemodialysis

Hemodialysis achieves clearance of blood solutes by convection and diffusion against a concentration gradient with dialysate flowing countercurrent to blood separated by a semipermeable dialyzer membrane. Hemodialysis is commonly performed three times per week for 3.5- to 4.5-hour treatment sessions at an outpatient dialysis unit. Frequent and/or longer treatments provide better control of volume status and serum electrolytes. In addition to the inconvenience of time spent in the dialysis unit, patients may have symptomatic hypotension during or following dialysis. Some patients also describe excessive fatigue following dialysis sessions. Some patients perform hemodialysis at home four to five times per week but with shorter treatment sessions.

Peritoneal Dialysis

Peritoneal dialysis utilizes an indwelling catheter to perform exchanges of dialysate into the peritoneum, which serves as a semipermeable membrane allowing for diffusion of solutes and osmosis of water. Dialysate is exchanged about three to five times per day to maintain a high concentration gradient and adequate solute clearance. Patients can perform exchanges during the day, or a cycler can be used to exchange the fluid overnight while the patient sleeps. Peritoneal dialysis allows greater autonomy. Patients can work or perform activities during the day. Clinical outcomes are similar for patients on peritoneal dialysis compared with hemodialysis, although patients starting RRT who have residual renal function may have better outcomes with peritoneal dialysis.

Peritonitis is a complication associated with increased morbidity and even mortality. Repeated infections can cause peritoneal damage, reducing the efficacy of the dialysis

TABLE 34. Goals of Care for Patients with End-Stage Kidney Disease Treated with Dialysis Versus Kidney Supportive Care

Issue	Current Disease-Focused Metrics for Conventional Delivery of Dialysis Care	Kidney Supportive Care
Vascular access	Creation and maintenance of an AVF; avoid central venous dialysis catheters as much as possible.	Central venous catheter acceptable if patient chooses hemodialysis.
Dialysis adequacy	Target small solute clearance based on current standards, intensifying the dialysis prescription as needed to achieve targets.	Lower clearance acceptable if changes in dialysis prescription increase demands inconsistent with patient preference; may involve fewer hemodialysis sessions or more frequent but shorter sessions.
Cardiovascular disease	Treat cardiovascular risk factors, including BP and dyslipidemia if indicated.	Tolerate hypertension to avoid symptoms; no indication for dyslipidemia treatment.
Mineral and bone disorder	Dietary counseling; binders to control hyperphosphatemia; vitamin D analogues with or without calcimimetics for secondary hyperparathyroidism.	Limited restrictions; more permissive hyperphosphatemia and hyperparathyroidism.
Nutrition	Encourage dietary protein intake while limiting potassium, sodium, and phosphorus intake.	Reduce dietary restrictions.
Laboratory monitoring	Routine monthly laboratory tests.	Minimal necessary.

AVF = arteriovenous fistula; BP = blood pressure.

treatments. Peritoneal dialysis–associated peritonitis is infrequent, with an average of one episode every 2 to 3 years. It is usually caused by gram-positive skin flora and less commonly by gram-negative intestinal flora. Proper skin hygiene and aseptic technique when handling the peritoneal dialysis catheter are critical in preventing peritonitis.

Non-Dialytic Palliative Therapy

Some patients with CKD stage G5 or ESKD may choose not to initiate RRT, or patients already on RRT may decide to discontinue treatment. Palliative care and hospice services play an important role in caring for these patients. Non-dialytic therapy is a reasonable treatment option for older patients with ESKD and multiple comorbidities. Treatment focuses on symptom management and results in less hospitalization with similar or better quality of life compared with patients on RRT. For patients who withdraw from RRT, death usually occurs within 2 weeks. Nineteen percent to 23% of patients withdraw from RRT before death. Patients who are older, White, or have multiple comorbid conditions are more likely to elect withdrawal.

KEY POINTS

- Clinical outcomes are similar for patients on peritoneal dialysis compared with hemodialysis.
- HVC Non-dialytic palliative therapy is a reasonable option for older patients with end-stage kidney disease and multiple comorbidities, with treatment focusing on symptom management and quality of life.

Kidney Transplantation

Kidney transplantation is the preferred treatment for ESKD. It improves life expectancy and quality of life, and provides significant cost savings to the health care system compared with dialysis. However, demand far exceeds supply, and waiting lists for deceased-donor kidneys are several years long in most regions of the United States.

Referral

Patients should be referred to a kidney transplant center for evaluation when the eGFR is 15 to 29 mL/min/1.73 m^2. Early referral is important because preemptive kidney transplants (transplants before needing dialysis) are associated with improved clinical outcomes compared with receiving a transplant after starting dialysis. Early referral also allows adequate time to identify suitable living donors.

Patients and donors undergo extensive health screening to identify issues that may affect the safety and/or outcome of the transplant. In the potential recipient, these include active malignancy, coronary artery disease, or infections. Adequate social support and financial resources are important to ensure medication adherence and long-term survival of the transplanted allograft. Donors are screened for intrinsic kidney disease, hypertension, and diabetes to ensure there is minimal risk related to reduced renal mass resulting from donation nephrectomy. Donors are at risk for future development of hypertension and proteinuria, with a small number of donors progressing to CKD. Blood pressure and kidney function of donors should be monitored as part of routine medical follow-up.

Patients are generally managed by a transplant nephrologist for at least the first 6 months posttransplant and are then co-managed with a general nephrologist and/or internist.

KEY POINTS

- For eligible patients, kidney transplantation is the preferred treatment for end-stage kidney disease because of improved mortality and quality of life and decreased health care cost. HVC

(Continued)

KEY POINTS *(continued)*

- Patients should be referred to a kidney transplant center for evaluation when the estimated glomerular filtration rate is 15 to 29 mL/min/1.73 m^2.
- Preemptive kidney transplants are associated with improved clinical outcomes compared with transplantation after dialysis.

Immunosuppressive Therapy

Immunosuppressive medications are required to prevent allograft rejection. Induction therapy is started perioperatively with polyclonal anti-T-cell antibodies (thymoglobulin) or monoclonal anti-interleukin-2 receptor antibody (basiliximab) in most patients. Calcineurin inhibitors with pulse glucocorticoids are also started.

Long-term maintenance therapy for most patients includes a combination of calcineurin inhibitors (tacrolimus or cyclosporine), antimetabolites (mycophenolate mofetil or azathioprine), and glucocorticoids. However, some patients with well-matched allografts can discontinue glucocorticoids. Doses of these medications are highest immediately posttransplant and are decreased over the next several months to minimize side effects (**Table 35**), including long-term nephrotoxicity, while maintaining adequate immunosuppression.

Calcineurin inhibitors are metabolized by the cytochrome P450 system. Drug-drug interactions may occur, leading to high or low levels of the calcineurin inhibitor and placing patients at risk for calcineurin toxicity or rejection. Care should be taken to check for potential interactions before adding new medications.

KEY POINT

- Potential drug-drug interactions with calcineurin inhibitors should be checked before adding new medications to avoid potential nontherapeutic or toxic drug levels.

Risks of Transplantation

Immediately posttransplant, patients need to be monitored for acute rejection and postoperative complications. Thereafter, minimizing risk for infection and medication side effects becomes the focus while maintaining adequate immunosuppression to prevent acute and chronic rejection.

Infection

Immunosuppression significantly increases the risk for infection. Within the first month after surgery, the most common infectious complications are similar to other surgeries and include urinary tract infections and wound infections. Afterward, opportunistic infections become more prevalent.

Cytomegalovirus (CMV) is an important pathogen. Risk for infection depends on the serologic status of the donor and recipient at the time of transplant. The highest risk occurs when a seropositive donor kidney is transplanted into a seronegative recipient. Most patients receive prophylaxis against CMV with valganciclovir during the first 6 to 12 months; however, CMV infections can occur after the medication is discontinued. Signs and symptoms include fever, leukopenia, pneumonitis, hepatitis, and gastroenteritis/colitis.

Prophylaxis against *Pneumocystis jirovecii* pneumonia with trimethoprim-sulfamethoxazole is commonly used. Atovaquone can be used for sulfa-allergic or hyperkalemic patients.

Polyoma BK virus uniquely affects kidney transplant patients, only rarely occurring with other organ transplants or in immunosuppressed states. The most common clinical manifestation is an acute or indolent rise in serum creatinine due to tubulointerstitial nephritis or ureteral stenosis. Treatment requires reduction in the immunosuppression dose, but this must be balanced against the risk of allograft rejection.

Patients with latent tuberculosis infection found on routine screening receive prophylactic therapy before transplant to minimize risk of reactivation in the immune-suppressed state.

TABLE 35. Common Side Effects of Medications Used for Chronic Maintenance Immunosuppression After Kidney Transplantation

Class	Medication	Common Side Effects
Calcineurin inhibitor	Cyclosporine	Hypertension; decreased GFR; dyslipidemia; hirsutism; gingival hyperplasia; tremor
	Tacrolimus	New-onset diabetes mellitus; decreased GFR; hypertension; gastrointestinal symptoms; tremor
Antimetabolite	Mycophenolate mofetil	Diarrhea; nausea/vomiting; leukopenia; anemia
	Azathioprine	Leukopenia; hepatitis; pancreatitis
mTOR inhibitor	Sirolimus	Proteinuria; dyslipidemia; new-onset diabetes mellitus; anemia; leukopenia; pneumonitis
	Everolimus	
Glucocorticoid	Prednisone	Osteopenia, osteoporosis, osteonecrosis; hypertension; edema; new-onset diabetes mellitus; glaucoma; cataracts

GFR = glomerular filtration rate.

Patients are screened for coccidioidomycosis before kidney transplant in endemic areas in the United States, namely the Southwestern region. Prophylactic therapy with fluconazole is initiated in patients with previous exposure.

Cancer

Because kidney transplant recipients are at higher risk for developing cancer, it is important to follow age- and sex-appropriate cancer screening guidelines before transplant. In addition, ultrasonography should be used to screen for renal cell carcinoma in patients on long-standing hemodialysis.

Immunosuppressive medications increase the risk for several forms of malignancy, with non-melanoma skin cancers being the most common. Therefore, transplant recipients should be screened regularly for skin in addition to age- and sex-specific cancers.

Posttransplant lymphoproliferative disorders can occur with long-term immunosuppression. These malignancies are caused by uncontrolled B-lymphocyte proliferation associated with Epstein-Barr virus infection and impaired T-cell surveillance. Treatment involves reduction in immunosuppression, administration of the anti-B-cell monoclonal antibody rituximab, and chemotherapy. Additionally, calcineurin inhibitors may be switched to sirolimus because of its antiproliferative effects.

Kaposi sarcoma is common and is associated with human herpesvirus-8 infection. Treatment involves reduction in immunosuppression dosing and switching to a sirolimus-based regimen.

KEY POINTS

- Within the first month following kidney transplantation, the most common infectious complications are similar to other surgeries and include urinary tract infections and wound infections; afterward, opportunistic infections (such as cytomegalovirus, *Pneumocystis jirovecii*, and polyoma BK virus) become more prevalent.
- Immunosuppression of kidney transplant recipients increases the risk for several malignancies, including non-melanoma skin cancers, Kaposi sarcoma, and posttransplant lymphoproliferative disorders; regular screening for skin and other age- and sex-specific cancers is recommended.

Special Considerations in Transplant Recipients

Acute Kidney Injury

AKI is a common posttransplant complication and can occur immediately posttransplant or any time in the future. Acute rejection should always be part of the differential diagnosis, because early recognition and treatment are associated with better long-term outcomes. Posttransplant AKI may also be due to renal vasoconstriction from calcineurin inhibitor toxicity, calcineurin inhibitor–induced thrombotic microangiopathy, BK nephropathy, ureteral stenosis, or any nontransplant-specific AKI cause.

Disease Recurrence

Glomerular diseases can recur in the transplant allograft. Focal segmental glomerulosclerosis is one of the most common forms of glomerular disease to recur posttransplant and can occur within days to weeks after transplantation. Focal segmental glomerulosclerosis and thrombotic microangiopathy should be treated aggressively if disease recurrence is seen in the transplanted kidney, because these conditions are associated with high rates of graft failure. Patients with lupus or ANCA vasculitis should have quiescent disease for several months preceding transplantation to reduce risk for disease recurrence. Diabetic kidney disease and IgA nephropathy may also affect allograft function after transplant.

Cardiovascular Disease

Cardiovascular disease is the leading cause of death in kidney transplant recipients. Kidney transplantation, despite restoration of kidney function, should be treated as a cardiovascular disease equivalent for purposes of risk factor modification.

Calcineurin inhibitors induce hypertension by activating the sodium chloride cotransporter in the distal convoluted tubule of the kidney. Therefore, thiazide diuretics may be efficacious in these patients. Dyslipidemia is a common side effect of calcineurin inhibitors, sirolimus, and glucocorticoids. Treatment with a statin improves cardiac outcomes; however, statins have drug-drug interactions with calcineurin inhibitors and can increase toxicity of both drugs.

Bone Disease

Secondary and tertiary hyperparathyroidism, common in patients with ESKD, can persist for several months posttransplant; continuation of vitamin D analogues or calcimimetics may be warranted if the patient is hypercalcemic. Additionally, hypophosphatemia secondary to hyperparathyroidism is common due to renal phosphorus wasting. Long-term glucocorticoids can cause osteopenia, osteoporosis, and osteonecrosis. Calcineurin inhibitors may also induce magnesium wasting. See Chronic Kidney Disease-Mineral and Bone Disorder for more information.

Vaccination

Most transplant centers do not recommend immunization within the first 3 to 6 months posttransplant because of increased immunosuppression and decreased likelihood of developing long-term immunity from the vaccine. Influenza vaccine, however, may be administered within 1 month of transplant in the setting of an influenza outbreak. Live attenuated vaccines are contraindicated in transplant recipients.

Hepatitis C Virus

The advent of safe and effective direct-acting antiviral agents for the treatment of hepatitis C virus (HCV) infection has opened the door to expanding the use of kidneys from HCV-positive donors. Some transplant centers are offering kidneys from HCV-positive donors to HCV-positive and HCV-negative recipients, and then treating the recipient for HCV after transplant.

Clinical trials have demonstrated successful cure of HCV infection in previously HCV-negative recipients of kidneys from HCV-positive donors. See MKSAP 19 Gastroenterology and Hepatology for more information about HCV.

HIV Infection

Successful kidney transplantation can be performed in recipients who have HIV infection that is controlled by antiretroviral medication. These patients should be referred to transplant centers with expertise in this area.

Complications of End-Stage Kidney Disease

Cardiovascular Disease

Sudden cardiac death is the leading cause of death in ESKD. This population is at increased risk because of rapid shifts of serum electrolytes during dialysis and chronic volume overload that contribute to left ventricular hypertrophy and cardiac fibrosis. Uremic toxins also contribute and may play a role in arrhythmogenesis. Avoiding rapid changes in serum potassium during dialysis may help limit arrhythmias, and adherence to dietary salt and fluid restriction may help limit volume overload. Intradialytic hypotension induced by rapid volume removal during dialysis may cause cardiovascular and central nervous system injury due to organ hypoperfusion. Vascular calcification is accelerated by uremic toxins, chronic inflammation, and calcium-based medications/vitamin D analogues. Limiting medications that raise serum calcium and achieving adequate clearance during dialysis may help delay the progression of atherosclerosis.

Infection

Infection is the second leading cause of death in ESKD. Patients are at increased risk because of a relatively immunosuppressed state from chronic inflammation and frequent exposure to the health care environment. Tunneled dialysis catheters increase the risk for bacteremia, and empiric antibiotics should be administered while waiting for blood culture results in patients with suspected bacteremia. Tunneled catheters should be removed for severe sepsis, evidence of metastatic infection, concomitant exit-site or tunnel infection, persistent fever, or bacteremia despite antibiotics. Exchange of the catheter over a guidewire is the best option for clinically stable patients without a tunnel infection or for patients who clear the bacteremia within 72 hours of antibiotic administration. Antibiotic lock therapy consists of instillation of a highly concentrated antibiotic solution into an intravascular catheter lumen during treatment of catheter-related bloodstream infections to salvage the catheter. Antibiotic lock therapy is an alternative for stable patients with less virulent gram-positive organisms. Prevention of catheter-associated infections is best achieved by minimizing need for their use through advanced planning to achieve functioning arteriovenous access.

Acquired Cystic Kidney Disease

Acquired cystic kidney disease is common among patients with severe CKD and ESKD. These cysts are at increased risk for transformation into renal cell carcinoma, but screening is not recommended for most patients with ESKD to avoid routine cancer screening for patients with limited life expectancy. Screening can be individualized for patients with longer life expectancy such as potential kidney transplant recipients. A high index of suspicion is warranted for patients with new gross hematuria, unexplained flank pain, or persistently elevated hemoglobin levels. For cysts that are highly suspicious for malignancy, partial nephrectomy and nephron-sparing approaches are indicated for less severe stages of CKD. For patients with advanced CKD or ESKD, radical nephrectomy is the most prudent option.

Calciphylaxis

Calciphylaxis (calcific uremic arteriolopathy), characterized by calcification of the vascular media, results in ischemic skin lesions and is an increasingly recognized complication of ESKD (**Figure 27**). Skin changes begin with induration and progress to tender subcutaneous plaques followed by frank necrosis. The lesions are painful and predict poor outcomes, including loss of mobility, hospitalization, sepsis, and death. Risk factors include secondary hyperparathyroidism, longer duration of dialysis, obesity, diabetes, and use of warfarin. There are no FDA-approved treatments. However, a number of

FIGURE 27. Calciphylaxis showing eschar with an angulated border on a patient's thigh. Note the central necrosis with surrounding erythema.

interventions are employed, including optimization of phosphate control, avoidance of calcium products and vitamin D analogues, initiation of calcimimetics, intravenous and intralesional sodium thiosulfate, and, in select cases, the use of direct anticoagulants in lieu of warfarin. Multidisciplinary care that includes wound management, dermatology, and plastic surgery is necessary.

Mental Health

Patients with CKD and ESKD are more likely to have depression and anxiety than the general population. The prevalence of depression is estimated to be 20% to 30% and is 12% to 52% for anxiety. Contributing factors may include illness burden and psychosocial factors, such as diminished social support. Depression is underrecognized in patients with ESKD, and data on treatment efficacy are limited. Treatment with behavioral therapy or selective serotonin reuptake inhibitors should be considered.

Symptoms Affecting Quality of Life

Patients with ESKD often have pruritus and sleep disturbance, including restless legs syndrome and obstructive sleep apnea (OSA). Because these are not life-threatening symptoms, they often receive less focus than other complications. However, they are significant contributors to diminished quality of life. The etiology of pruritus is not known but may include inflammation or increased activity of skin opioid receptors. Twenty percent to 80% of patients with ESKD have pruritis. Extensive research is lacking, but treatment with gabapentin has shown the most evidence for efficacy in symptom relief.

Sleep disturbance is common among patients with ESKD and can be improved with increased intensity of dialysis, which should be the first-line therapy followed by other therapies used in patients without ESKD. Restless legs syndrome is estimated to affect approximately 20% and OSA up to 50% of patients with ESKD. As in the general population, OSA is associated with increased mortality. Symptoms of OSA in a patient with ESKD should prompt evaluation and treatment if the diagnosis is confirmed.

KEY POINTS

- Complications of end-stage kidney disease include cardiovascular disease, infection, acquired cystic kidney disease, calciphylaxis, and depression.
- Patients with end-stage kidney disease often have symptoms that impair quality of life such as pruritus and sleep disturbance, including restless legs syndrome and obstructive sleep apnea.

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Nephrology Self-Assessment Test

This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American College of Physicians designates MKSAP 19 Nephrology for a maximum of 27 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of the CME activity, which includes participation in the evaluation component, enables the participant to earn up to 27 medical knowledge MOC points in the American Board of Internal Medicine's Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

Earn Credits or MOC Points Online

To earn CME credits or to apply for MOC points, MKSAP users need to answer at least one of two questions correctly (earning a score of at least 50%) and click the Submit CME button. Each single MKSAP 19 self-assessment question qualifies for one quarter of a CME credit hour or ABIM MOC point.

MKSAP 19 Subscribers can enter their self-assessment question answers and submit for CME/MOC in two ways:

1. Users of MKSAP 19 Complete who prefer to use their print books and a paper answer sheet to study and record their answers can use the printed answer sheet at the back of this book to record their answers. The corresponding online answer sheets, which are available on the MKSAP 19 Resource Page, may be used to transcribe answers onto the online answer sheets. Users may then submit their answers to qualify for CME credits or MOC points (see below for information on Opting in for MOC). Users who prefer to record their answers on a paper answer sheet should save their answer sheet for future use. Users who study with MKSAP 19 print can also submit their answers directly within MKSAP 19 Digital by accessing the self-assessment questions dashboard and selecting the preferred subspecialty section to begin answering questions.
2. Users of MKSAP 19 Digital can enter their answers within the digital program by accessing the self-assessment questions dashboard and selecting the preferred subspecialty section to begin answering questions and clicking the Submit CME button once they qualify for CME and are ready to submit. Learners should keep in mind their yearly CME and MOC deadlines when determining the appropriate time to submit.

Learners' CME/MOC submission progress will be shown on the MKSAP 19 Digital CME/MOC/CPD page.

Opting in for MOC

MKSAP 19 users can opt in for simultaneous submission of CME and MOC points as they answer self-assessment questions. To opt in, users will be required to complete a form requesting their name, date of birth, and ABIM number. The MOC Opt-in Form will be presented upon the user's first CME submission and needs to be completed only once.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

An 18-year-old man is evaluated in the emergency department for a severe asthma exacerbation unresponsive to intensification of his home program of albuterol and fluticasone-salmeterol inhalers. Intravenous magnesium sulfate, prednisone, and inhaled albuterol are initiated.

On physical examination, the patient is in respiratory distress. Blood pressure is 145/88 mm Hg, respiratory rate is 32/min, pulse is 108/min, and oxygen saturation is 95% with the patient breathing ambient air. Pulmonary examination reveals diffuse wheezes. The remainder of the examination is unremarkable.

Laboratory studies:

Electrolytes:	
Sodium	140 mEq/L (140 mmol/L)
Potassium	3.2 mEq/L (3.2 mmol/L)
Chloride	110 mEq/L (110 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)
Glucose	124 mg/dL (6.9 mmol/L)
Arterial blood gases:	
pH	7.50
P_{CO_2}	32 mm Hg (4.2 kPa)
P_{O_2}	77 mm Hg (10.2 kPa)

Which of the following is the most likely cause of this patient's hypokalemia?

(A) Albuterol
(B) Hyperglycemia
(C) Hypermagnesemia
(D) Prednisone
(E) Respiratory alkalosis

Item 2

A 63-year-old woman is hospitalized for cardiac catheterization for unstable angina. History is significant for stage G3 chronic kidney disease attributed to diabetic nephropathy. Medications are heparin, metoprolol, losartan, amlodipine, atorvastatin, basal insulin, and prandial insulin.

On physical examination, vital signs are normal. There is no jugular venous distension or lower extremity edema. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 2.4 mg/dL (212.2 µmol/L) and an estimated glomerular filtration rate of 24 mL/min/1.73 m^2.

Which of the following is the most appropriate periprocedure measure to prevent acute kidney injury?

(A) Hemodialysis, postprocedure
(B) Intravenous isotonic bicarbonate, pre- and postprocedure
(C) Intravenous 0.9% saline, pre- and postprocedure
(D) Oral N-acetylcysteine, preprocedure

Item 3

A 69-year-old man is evaluated for a 4-week history of lower extremity edema. He has a 45-pack-year history of smoking but quit 3 years ago. A screening colonoscopy performed 1 year ago was normal. He has no other medical history and takes no medications.

On physical examination, vital signs are normal. There is 2-mm pitting edema of the lower extremities through the ankles, equal on both sides. The remainder of the examination is unremarkable.

Laboratory studies:

Albumin	2.9 g/dL (29 g/L)
Total cholesterol	311 mg/dL (8.1 mmol/L)
Creatinine	1.0 mg/dL (88.4 µmol/L)
24-Hour urine protein excretion	6300 mg/24 h

Kidney biopsy shows membranous nephropathy with negative staining for the phospholipase A2 receptor antigen.

Which of the following is the most appropriate test to perform next?

(A) Kidney and renal vein Doppler ultrasonography
(B) Lower extremity Doppler ultrasonography
(C) Noncontrast CT of the chest
(D) Random (spot) urine protein-creatinine ratio

Item 4

A 54-year-old woman is evaluated during a follow-up visit after beginning lisinopril for hypertension 2weeks ago. History is also significant for chronic kidney disease. Her only other medication is amlodipine.

On physical examination, blood pressure is 128/78 mm Hg; other vital signs are normal. There is 1+ pitting pretibial edema bilaterally. The remainder of the examination is unremarkable.

Laboratory studies:

Creatinine	1.7 mg/dL (150.3 µmol/L); 2 weeks ago: 1.2 mg/dL (106.1 µmol/L)
Potassium	5.7 mEq/L (5.7 mmol/L); 2 weeks ago: 4.4 mEq/L (4.4 mmol/L)
Estimated glomerular filtration rate	33 mL/min/1.73 m^2; 2 weeks ago, 50 mL/min/1.73 m^2

Two weeks ago, laboratory studies showed a urine albumin-creatinine ratio of 1600 mg/g.

Which of the following is the most appropriate management?

(A) Continue lisinopril; add furosemide
(B) Continue lisinopril; recheck laboratory studies in 2 weeks
(C) Discontinue lisinopril; add furosemide
(D) Discontinue lisinopril; add losartan

Item 5

A 32-year-old man is evaluated for end-stage kidney disease due to congenital reflux nephropathy. He began hemodialysis at age 21 years. He is on the kidney transplant list. He also has hypertension. Medications are amlodipine, calcitriol, lisinopril, and sevelamer carbonate.

On physical examination, vital signs are normal. There is a left upper extremity arteriovenous fistula with strong thrill. The remainder of the examination is normal.

Kidney ultrasound shows small kidneys with multiple cysts bilaterally. A few cysts have internal septations. There are no solid components or evidence of vascular flow within the cysts.

Which of the following is the most appropriate management of this patient's acquired kidney cysts?

(A) Annual kidney ultrasonography
(B) Bilateral nephrectomy
(C) Tolvaptan therapy
(D) No intervention

Item 6

A 69-year-old woman is evaluated for a 2-month history of worsening fatigue, weight loss, and anorexia. She has no other medical problems and takes no medications.

On physical examination, the patient is afebrile. Blood pressure is 160/95 mm Hg, pulse rate is 88/min, respiration rate is 16/min, and oxygen saturation is 100% breathing ambient air. The remainder of the examination is unremarkable.

Laboratory studies:

Hematocrit	25.5%
Albumin	3.7 g/dL (37 g/L)
Calcium	10.9 mg/dL (2.7 mmol/L)
Creatinine	4.2 mg/dL (371.3 µmol/L)
Free κ light chains	Elevated
Free λ light chains	Elevated
κ/λ Free light chain ratio	4.1 (normal, 0.26-1.65)
Urinalysis	No blood; 1+ protein
Urine protein-creatinine ratio	2500 mg/g
Urine output	2.3 L/24 h

Kidney biopsy confirms the presence of myeloma cast nephropathy.

Which of the following is the most appropriate management?

(A) Chemotherapy
(B) Hemodialysis
(C) Hospice referral
(D) Plasmapheresis

Item 7

A 52-year-old man is evaluated during a follow-up visit for membranous nephropathy diagnosed by kidney biopsy 1 month ago. His medical history is otherwise unremarkable. Medications are lisinopril, furosemide, and atorvastatin.

On physical examination, vital signs are normal. There is symmetric 2+ pitting edema of the lower extremities. The remainder of the examination is unremarkable.

Laboratory studies:

Albumin	2.1 g/dL (21 g/L)
Total cholesterol	359 mg/dL (9.3 mmol/L)
Creatinine	0.8 mg/dL (70.7 µmol/L)
Urine protein-creatinine ratio	5500 mg/g

Which of the following is the most likely complication to develop in this patient during the next 12 months?

(A) Diabetes mellitus
(B) End-stage kidney disease
(C) Pulmonary hemorrhage
(D) Venous thromboembolism

Item 8

A 53-year-old woman is evaluated for an increase in her serum creatinine level. History is significant for long-standing hypertension treated with lisinopril. She reports no changes to her medication regimen during the past year.

On physical examination, blood pressure is 145/92 mm Hg, and pulse rate is 84/min; other vital signs are normal. The remainder of the examination is unremarkable.

Laboratory studies:

Creatinine	1.2 mg/dL (106.1 µmol/L); 6 months ago: 0.7 mg/dL (61.9 µmol/L)
Estimated glomerular filtration rate	>52 mL/min/1.73 m^2
Urinalysis	Specific gravity 1.014; pH 5.7; no blood; trace protein
Urine albumin-creatinine ratio	290 mg/g

Ultrasound reveals normal-sized kidneys with increased echogenicity; no hydronephrosis or abnormalities of the collecting system are seen.

Which of the following is the most appropriate management?

(A) Obtain kidney biopsy
(B) Obtain random urine protein-creatinine ratio
(C) Recheck serum creatinine in 3 months
(D) Substitute hydrochlorothiazide for lisinopril

Item 9

A 24-year-old woman is evaluated in the hospital 24 hours after being admitted for severe preeclampsia. On admission, antihypertensive therapy and intravenous magnesium sulfate were initiated followed by cesarean section. She continues to receive hydralazine, nifedipine, and intravenous magnesium sulfate.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 142/90 mm Hg, and pulse rate is 84/min. Abdominal examination reveals a clean, sutured cesarean section incision without bleeding. There is no oozing from venipuncture sites. There is 1+ lower extremity edema. The remainder of the examination is unremarkable.

H CONT.

Current laboratory studies:

Hemoglobin	7.5 g/dL (75 g/L)
Platelet count	84,000/μL (84×10^9/L)
Alanine aminotransferase	383 U/L
Aspartate aminotransferase	187 U/L
Creatinine	1.3 mg/dL (114.9 μmol/L)

A peripheral blood smear shows schistocytes.

Which of the following is the most appropriate treatment?

(A) Continue current therapy
(B) Start intravenous dexamethasone
(C) Start intravenous eculizumab
(D) Transfuse fresh frozen plasma
(E) Transfuse packed red blood cells and platelets

Item 10

A 63-year-old man is evaluated during a follow-up visit for gastroesophageal reflux disease and heartburn. His symptoms are worse after large meals and when lying down and have significantly decreased the quality of his life and disrupted his sleep. He also has stage G4 chronic kidney disease, obesity, and hypertension. Medications are atenolol, lisinopril, and nifedipine.

On physical examination, vital signs are normal. BMI is 38. The remainder of the examination is normal.

Laboratory studies show an estimated glomerular filtration rate of 29 mL/min/1.73 m^2.

Weight loss and other lifestyle management modifications for gastroesophageal reflux disease are discussed.

Which of the following is the most appropriate additional therapy?

(A) Famotidine
(B) Omeprazole
(C) Oral calcium carbonate and magnesium hydroxide
(D) Sucralfate

Item 11

A 38-year-old woman is evaluated in the emergency department for a 4-hour history of left flank pain that radiates to the groin. She is otherwise well and takes no medications.

A noncontrast helical CT scan of the abdomen shows a 11-mm stone in the proximal ureter. There is dilation of the renal calyces.

Analgesics are initiated.

Which of the following is the most appropriate additional treatment?

(A) Intravenous 0.9% saline
(B) Lithotripsy
(C) Tamsulosin
(D) Observation

Item 12

A 45-year-old woman is evaluated in the emergency department for a 3-day history of lower extremity weakness. Medical history is significant for hypertension, type 2 diabetes mellitus, and gastroesophageal reflux disease. Medications are lisinopril, metformin, canagliflozin, and pantoprazole.

On physical examination, vital signs are normal. Knee and ankle reflexes are decreased. Muscle strength is 4/5 in the lower extremities. The remainder of the examination is unremarkable.

Laboratory studies:

Creatinine	1.1 mg/dL (97.2 μmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	3.0 mEq/L (3.0 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	23 mEq/L (23 mmol/L)
Magnesium	1.1 mg/dL (0.45 mmol/L)

Which of the follow is the most likely cause of this patient's hypokalemia?

(A) Canagliflozin
(B) Lisinopril
(C) Pantoprazole
(D) Surreptitious diuretic use

Item 13

A 32-year-old woman is referred by the public health department for elevated blood pressure measurements during pregnancy. She is at 24 weeks' gestation of her first pregnancy. Records document blood pressure measurements averaging 140/90 mm Hg before pregnancy. She did not have routine medical care before her pregnancy. Her only medication is a prenatal vitamin.

On physical examination, blood pressure is 154/92 mm Hg; other vital signs are normal. The patient has a gravid uterus consistent with her stage of pregnancy. There is trace ankle edema bilaterally. Funduscopic, cardiac, and neurologic examinations are normal.

Laboratory studies are normal; urinalysis shows no proteinuria.

ECG is normal.

Which of the following is the most appropriate management for this patient's hypertension?

(A) Early delivery of the fetus
(B) Start hydrochlorothiazide
(C) Start labetalol
(D) Clinical monitoring

Item 14

A 34-year-old woman is evaluated for hypertension. During the past 3 months, two blood pressure measurements in health care settings averaged 150/90 mm Hg. During the same time period, three blood pressure measurements obtained outside of health care settings averaged 128/78 mm Hg.

She has no other pertinent personal or family history. She takes no medications.

On physical examination, blood pressure is 144/92 mm Hg in both arms, pulse rate is 80/min, and respiration rate is 18/min. BMI is 22. The remainder of the examination is normal.

Which of the following is the most appropriate management?

(A) Begin chlorthalidone
(B) Obtain renal artery imaging
(C) Perform ambulatory blood pressure monitoring
(D) Recheck blood pressure in the office in 3 months

Item 15

A 68-year-old man is evaluated in the emergency department for generalized weakness that began 12 hours ago after ingesting a bottle of magnesium citrate for constipation. He has hypertension, hyperlipidemia, and stage G4 chronic kidney disease. Medications are furosemide, nifedipine, and simvastatin.

On physical examination, blood pressure is 102/64 mm Hg, and pulse rate is 50/min; other vital signs are normal. Muscle strength is 4/5 diffusely. Reflexes are absent throughout. The remainder of the examination is normal.

Laboratory studies:

Calcium	8.4 mg/dL (2.1 mmol/L)
Creatinine	5.5 mg/dL (486.2 µmol/L)
Magnesium	6.8 mg/dL (2.8 mmol/L)
Phosphorus	5.5 mg/dL (1.8 mmol/L)

Which of the following is the most appropriate immediate treatment?

(A) Intravenous calcium gluconate
(B) Intravenous furosemide
(C) Intravenous sodium bicarbonate
(D) Oral patiromer

Item 16

A 77-year-old woman is evaluated in the ICU for acute kidney injury after being hospitalized 2 days ago for septic shock and acute respiratory distress syndrome secondary to community-acquired pneumonia. She was intubated and vasopressor support was initiated. Over the first 18 hours of hospitalization, she received 3600 mL of Ringer's lactate solution. Current medications are norepinephrine, ceftaroline, levofloxacin, and dexmedetomidine.

On physical examination, the patient is mechanically ventilated. Temperature is 38.4 °C (101.1 °F), blood pressure is 88/52 mm Hg, pulse rate is 105/min, respiration rate is 16/min, and oxygen saturation is 90% with the patient breathing 50% FIO_2. Diffusely coarse breath sounds are heard on pulmonary examination. A central venous catheter is in place; central venous pressure measurement is 14 mm Hg.

Urine output is 30 mL/h and unresponsive to escalating doses of intravenous furosemide.

Current laboratory studies:

Creatinine	3.4 mg/dL (300.6 µmol/L)
Electrolytes:	
Sodium	134 mEq/L (134 mmol/L)
Potassium	6.4 mEq/L (6.4 mmol/L)
Chloride	100 mEq/L (100 mmol/L)
Bicarbonate	12 mEq/L (12 mmol/L)

Chest radiograph shows diffuse bilateral infiltrates and vascular cephalization.

Which of the following is the most appropriate therapy?

(A) Begin continuous renal replacement therapy
(B) Begin peritoneal dialysis
(C) Continue current management
(D) Switch to intravenous bumetanide

Item 17

A 23-year-old woman is evaluated for a 1-week history of muscle weakness. Medical history is significant for chronic migraine headaches. Medications are topiramate, sumatriptan, naproxen, and aspirin.

On physical examination, vital signs are normal. BMI is 19. The remainder of the examination is unremarkable.

Laboratory studies:

Electrolytes:	
Sodium	142 mEq/L (142 mmol/L)
Potassium	3.1 mEq/L (3.1 mmol/L)
Chloride	120 mEq/L (120 mmol/L)
Bicarbonate	15 mEq/L (15 mmol/L)
Urine sodium	18 mEq/L (18 mmol/L)
Urine potassium	8.0 mEq/L (8.0 mmol/L)
Urine chloride	32 mEq/L (32 mmol/L)

Which of the following is the most likely cause of this patient's metabolic acidosis?

(A) Salicylate toxicity
(B) Surreptitious furosemide use
(C) Surreptitious laxative use
(D) Topiramate

Item 18

A 57-year-old man is evaluated during a follow-up visit for stable chronic kidney disease diagnosed 1 year ago. Renal duplex Doppler ultrasound at that time showed a 7-cm right kidney and 11-cm left kidney with a >75% midstenotic lesion of the left renal artery. He also has type 2 diabetes mellitus, hyperlipidemia, and peripheral artery disease. Medications are low-dose aspirin, furosemide, lisinopril, amlodipine, carvedilol, metformin, empagliflozin, and atorvastatin.

On physical examination, blood pressure is 128/74 mm Hg, pulse rate is 65/min, and respiration rate is 18/min. Bilateral carotid and lower abdominal quadrant bruits are heard. Peripheral extremity pulses are diminished. The remainder of the examination is normal.

Laboratory studies:

Creatinine	1.4 mg/dL (123.8 µmol/L)
Electrolytes	Normal
Estimated glomerular filtration rate	45 mL/min/1.73 m^2
Urine albumin-creatinine ratio	1100 mg/g

Which of the following is the most appropriate management?

(A) Left renal artery angioplasty
(B) Renal artery CT angiography
(C) Renal artery MR angiography
(D) No additional diagnostic testing

Item 19

A 46-year-old woman is evaluated for a serum creatinine level of 2.6 mg/dL (229.8 µmol/L). Her baseline serum creatinine level 3 months ago was 0.9 mg/dL (79.6 µmol/L). She has no symptoms. Two years ago, she started losartan and amlodipine for hypertension. One year ago, she started omeprazole for gastroesophageal reflux disease and naproxen for knee osteoarthritis. Eight months ago, she began atorvastatin for hyperlipidemia.

On physical examination, temperature is 37.0 °C (98.6 °F), and blood pressure is 138/86 mm Hg. The remainder of the examination is unremarkable.

Urinalysis shows the following: specific gravity 1.015; pH 5.5; 1+ erythrocytes; 3+ leukocytes; 1+ leukocyte esterase; no nitrates; and >100 leukocytes/hpf with leukocyte and granular casts.

Which of the following drugs should be discontinued in this patient?

(A) Atorvastatin and amlodipine
(B) Losartan and amlodipine
(C) Losartan and omeprazole
(D) Naproxen and atorvastatin
(E) Naproxen and omeprazole

Item 20

A 56-year-old man is evaluated for weakness after completing a second cycle of chemotherapy for a soft-tissue sarcoma recently excised from the right thigh. Medications are ifosfamide, doxorubicin, and mesna.

On physical examination, vital signs are normal. The patient appears well. Generalized weakness is noted. There is a healing surgical scar on the upper right thigh. The remainder of the examination is normal.

Laboratory studies:

Creatinine	1.6 mg/dL (141.4 µmol/L)
Electrolytes:	
Sodium	136 mEq/L (136 mmol/L)
Potassium	3.5 mEq/L (3.5 mmol/L)
Chloride	106 mEq/L (106 mmol/L)
Bicarbonate	18 mEq/L (18 mmol/L)
Glucose	88 mg/dL (4.9 mmol/L)
Phosphorus	1.2 mg/dL (0.39 mmol/L)
Fractional excretion of phosphorus	10%
Urinalysis	pH 7.0; no blood; 3+ protein; 2+ glucose; no leukocyte esterase

Which of the following is the most likely cause of this patient's hypophosphatemia?

(A) Chronic kidney disease
(B) Increased fibroblast growth factor 23 production
(C) Intracellular shift of phosphorus
(D) Osmotic diuresis
(E) Proximal renal tubular dysfunction

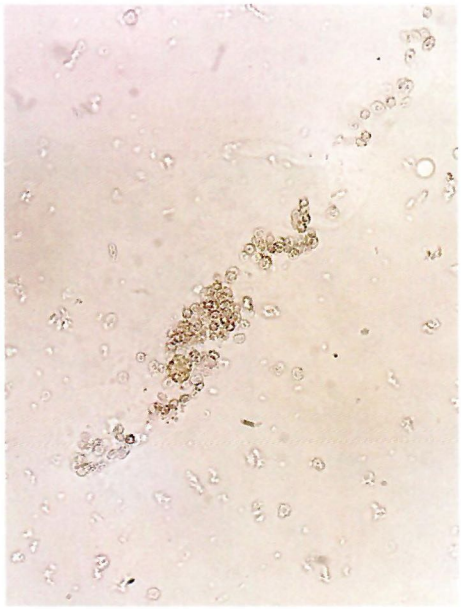
Item 21

A 25-year-old woman is evaluated for a 6-month history of fatigue, joint pain, sun sensitivity, and pleuritic chest pain. Medications are an oral contraceptive pill and as-needed naproxen.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 142/90 mm Hg, and pulse rate is 100/min. The fingers and wrist joints are tender, but there is no synovitis. The remainder of the examination is normal.

Laboratory studies show a serum creatinine level of 1.4 mg/dL (123.8 µmol/L); dipstick urinalysis shows 2+ blood, 3+ protein, positive leukocyte esterase, and no nitrites.

Urine microscopy is shown.



Which of the following is the most appropriate test?

(A) Cystoscopy
(B) Kidney biopsy
(C) Kidney ultrasonography
(D) Urine culture

Item 22

A 42-year-old man is evaluated during a follow-up visit for recently confirmed primary hypertension. Hypertension was confirmed with multiple home blood pressure monitoring readings that averaged 148/98 mm Hg. Chlorthalidone was initiated 1 month ago, and home blood pressure monitoring showed readings above target despite adherence to

lifestyle interventions and medication. He has no other medical problems and takes no other medication. The patient is Black.

On physical examination, blood pressure is 144/94 mm Hg, and pulse rate is 72/min; other vital signs are normal. BMI is 22. The remainder of the examination is normal.

Laboratory studies show a serum creatinine level of 1.0 mg/dL (88.4 µmol/L) and a serum potassium level of 3.5 mEq/L (3.5 mmol/L).

Which of the following is the most appropriate additional treatment?

(A) Amlodipine
(B) Doxazosin
(C) Hydralazine
(D) Metoprolol

Item 23

A 73-year-old woman is evaluated during a follow-up visit for stage G4 chronic kidney disease. She reports no uremic symptoms. Medical history is also significant for hypertension. Medications are atenolol, chlorthalidone, cholecalciferol, hydralazine, and nifedipine.

The physical examination, including vital signs, is normal.

Laboratory studies:

Calcium	8.7 mg/dL (2.2 mmol/L)
Creatinine	2.0 mg/dL (176.8 µmol/L)
Phosphorus	5.4 mg/dL (1.7 mmol/L)
Parathyroid hormone	97 pg/mL (97 ng/L)
25-hydroxyvitamin D	60 ng/mL (150 nmol/L)
Estimated glomerular filtration rate	24 mL/min/1.73 m^2

Which of the following is the most appropriate management?

(A) Calcitriol
(B) Calcium acetate
(C) Cinacalcet
(D) Low phosphate diet
(E) Sevelamer

Item 24

A 35-year-old man is evaluated during a follow-up visit for an elevated serum creatinine level. The elevated serum creatinine was discovered during a recent hospitalization for cellulitis of the right lower leg that was treated with intravenous cephazolin followed by oral cephalexin for a total of 7 days of antibiotic therapy. He is a migratory agricultural worker. He works in the northeastern United States during summer months and returns to Guatemala for the remainder of the year performing similar work. The patient has no other medical problems and takes no medications.

On physical examination, blood pressure is 138/90 mm Hg; other vital signs are normal. BMI is 27. The remainder of the examination is normal.

Laboratory studies:

Creatinine	2.0 mg/dL (176.8 µmol/L)
Electrolytes:	
Sodium	140 mEq/L (140 mmol/L)
Potassium	5.0 mEq/L (5.0 mmol/L)
Chloride	112 mEq/L (112 mmol/L)
Bicarbonate	18 mEq/L (18 mmol/L)
Urinalysis	Specific gravity 1.015; pH 6.5; no blood; 1+ protein; 1+ leukocytes; 2-5 leukocytes/hpf; 0-2 erythrocytes/hpf; no casts
Urine protein-creatinine ratio	400 mg/g

Kidney ultrasound shows a 9.9-cm right kidney and a 10.3-cm left kidney with increased cortical echogenicity and mild thinning; there is no hydronephrosis.

Which of the following is the most likely diagnosis?

(A) Acute interstitial nephritis
(B) Acute tubular necrosis
(C) Chronic interstitial nephritis
(D) IgA nephropathy
(E) Infection-related glomerulonephritis

Item 25

H

A 48-year-old woman is evaluated in the ICU for increasing serum creatinine and oliguria; she has cirrhosis. She was hospitalized 24 hours ago and treated for a bleeding esophageal varix. Outpatient medications are furosemide, spironolactone, nadolol, and norfloxacin. On admission, her serum creatinine level was 1.5 mg/dL (132.6 µmol/L).

On physical examination, blood pressure is 102/63 mm Hg, and pulse rate is 66/min; other vital signs are normal. Ascites and jaundice are present. The remainder of the examination is normal.

Urine output is 190 mL over the past 24 hours.

Current laboratory studies:

Albumin	2.3 g/dL (23 g/L)
Creatinine	2.3 mg/dL (203.3 µmol/L)
Electrolytes:	
Sodium	126 mEq/L (126 mmol/L)
Potassium	3.9 mEq/L (3.9 mmol/L)
Chloride	95 mEq/L (95 mmol/L)
Bicarbonate	18 mEq/L (18 mmol/L)
Urine sodium	<10 mEq/L (10 mmol/L)
Urinalysis	Specific gravity 1.030; pH 5.0; trace protein; 2+ bilirubin; bilirubin staining; no erythrocytes or leukocytes

Kidney ultrasound shows normal-appearing kidneys without hydronephrosis.

Diuretics are withheld, and norepinephrine infusion is initiated.

Which of the following is the most appropriate additional treatment?

(A) Hemodialysis
(B) Intravenous albumin
(C) Oral midodrine and intravenous octreotide
(D) Transjugular intrahepatic portosystemic shunt

Item 26

A 43-year-old man is evaluated during a routine follow-up visit for end-stage kidney disease due to IgA nephropathy. He received a living-donor related kidney transplant 5 years ago. He is asymptomatic. Medical history is also significant for hypertension. Medications are prednisone, mycophenolate mofetil, tacrolimus, lisinopril, metoprolol, and atorvastatin.

All physical examination findings, including vital signs, are normal.

Laboratory studies show a serum creatinine level of 0.8 mg/dL (70.7 µmol/L) and a fasting blood glucose level of 99 mg/dL (5.5 mmol/L).

Which of the following is the most appropriate screening test at this time?

(A) Colonoscopy
(B) Low-dose chest CT
(C) Oral glucose tolerance test
(D) Skin examination

Item 27

A 43-year-old man is evaluated during a follow-up visit for a recent biopsy-confirmed diagnosis of IgA nephropathy. He is asymptomatic. He has no other medical problems and takes no medications.

Physical examination findings, including vital signs, are normal.

Laboratory studies:

Albumin	4.0 g/dL (40 g/L)
Creatinine	0.95 mg/dL (84 µmol/L)
Urinalysis	3+ blood; 2+ protein
24-Hour urine protein excretion	725 mg/24 h

Which of the following is the most appropriate management?

(A) Lisinopril
(B) Mycophenolate mofetil
(C) Omega-3 fatty acids
(D) Prednisone

Item 28

A 22-year-old woman participating in a marathon is evaluated in the medical tent for headache, confusion, and disorientation after she stopped running at mile 20. This is her first marathon.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 110/72 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. The patient is confused. The remainder of the examination is normal.

Laboratory studies show a serum sodium level of 130 mEq/L (130 mmol/L).

Which of the following is the most appropriate management?

(A) Fluid restriction
(B) Intravenous 0.9% saline
(C) 100-mL bolus of 3% saline
(D) No treatment

Item 29

A 54-year-old man is evaluated during a new patient visit. He has a 30-year history of type 2 diabetes mellitus and 10-year history of hypertension. Medical history is also significant for obesity and hypercholesterolemia. Medications are amlodipine, atorvastatin, canagliflozin, metformin, and lisinopril-hydrochlorothiazide. At his last visit to his previous physician, serum creatinine level was 1.4 mg/dL (123.8 µmol/L), and estimated glomerular filtration rate was 58 mL/min/1.73 m^2.

On physical examination, blood pressure is 158/82 mm Hg, and pulse rate is 62/min; other vital signs are normal. BMI is 38. The remainder of the examination is normal.

Laboratory studies:

Albumin	3.5 g/dL (35 g/L)
Creatinine	1.6 mg/dL (141.4 µmol/L)
Electrolytes	Normal
Estimated glomerular filtration rate	50 mL/min/1.73 m^2
Urinalysis	No blood; 2+ protein

Results of kidney ultrasonography and referral to an ophthalmologist for a dilated retinal examination are pending.

Which of the following is the most appropriate test to assess the prognosis of this patient's chronic kidney disease?

(A) Hemoglobin A_{1c} measurement
(B) Kidney biopsy
(C) Serum parathyroid hormone measurement
(D) Spot urine albumin-creatinine ratio

Item 30

H

A 62-year-old man is evaluated in the emergency department for abrupt onset of sharp chest pain radiating to his upper back that started 90 minutes ago. Medical history includes difficult-to-control hypertension, hyperlipidemia, and type 2 diabetes mellitus. Medications are metformin, empagliflozin, rosuvastatin, amlodipine, hydrochlorothiazide, and lisinopril.

On physical examination, blood pressure is 210/120 mm Hg in the right arm and 180/100 mm Hg in the left arm, pulse rate is 118/min, respiration rate is 20/min, and oxygen saturation is 97% with the patient breathing ambient air. The patient is diaphoretic and in distress. Cardiac examination reveals tachycardia with a 3/6 diastolic murmur heard along the upper left sternal border. Lungs are clear to auscultation. The remainder of the examination is unremarkable.

Emergency CT imaging confirms the diagnosis of ascending aortic dissection.

Referral for emergency surgical consultation is obtained.

Which of the following is the most appropriate initial intravenous treatment?

(A) Esmolol
(B) Hydralazine
(C) Nicardipine
(D) Nitroprusside

Item 31

A 65-year-old man is evaluated for fatigue and weakness progressing over the last 3 months. His medical history is otherwise unremarkable, and he takes no medications.

Findings on physical examination, including vital signs, are normal.

Laboratory studies:

Hemoglobin	9 g/dL (90 g/L)
Albumin	3.0 g/dL (30 g/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	3.4 mEq/L (3.4 mmol/L)
Chloride	118 mEq/L (118 mmol/L)
Bicarbonate	14 mEq/L (14 mmol/L)
Glucose	74 mg/dL (4.1 mmol/L)
Phosphorus	2.1 mg/dL (0.7 mmol/L)
Total protein	8.0 g/dL (80 g/L)
Urinalysis	pH 5.0; no blood; no protein; no erythrocytes; 1+ leukocytes; trace glucose

Which of the following is the most likely cause of this patient's laboratory findings?

(A) Bartter syndrome
(B) Liddle syndrome
(C) Type 1 (hypokalemic distal) renal tubular acidosis
(D) Type 2 (proximal) renal tubular acidosis
(E) Type 4 (hyperkalemic distal) renal tubular acidosis

Item 32

A 46-year-old man is evaluated for confirmed primary hypertension. The patient is asymptomatic and takes no medications. He is a current smoker with a 20-pack-year history. Family history is significant for hypertension in his mother and father; his father had a stroke at age 55 years.

On physical examination, blood pressure is 154/96 mm Hg in both arms, pulse rate is 74/min, and respiration rate is 18/min. BMI is 30. The remainder of the examination is normal.

Laboratory studies:

Fasting lipid profile:	
Total cholesterol	220 mg/dL (5.7 mmol/L)
LDL cholesterol	160 mg/dL (4.1 mmol/L)
HDL cholesterol	48 mg/dL (1.2 mmol/L)
Creatinine	1.0 mg/dL (88.4 µmol/L)
Electrolytes	Normal
Glucose, fasting	80 mg/dL (4.4 mmol/L)
Urinalysis	No protein, erythrocytes, or leukocytes

A 12-lead ECG is normal.

The patient is instructed in lifestyle modifications, including smoking cessation, exercise, and a low sodium diet. Moderate-intensity atorvastatin is initiated.

Which of the following is the most appropriate additional therapy?

(A) Amlodipine
(B) Amlodipine-valsartan
(C) Chlorthalidone
(D) Valsartan

Item 33

A 43-year-old man is evaluated for one episode of gross hematuria 3 days ago. He reports no flank pain and no associated trauma on exertion. Medical history is otherwise unremarkable. He does not smoke cigarettes and takes no medications.

Physical examination findings, including vital signs, are normal.

Laboratory studies:

Blood urea nitrogen	Normal
Creatinine	Normal
Urinalysis	No protein; 1+ heme pigment; 10-15 erythrocytes/hpf; 0-2 leukocytes/hpf; no nitrites; no leukocyte esterase
Random urine protein-creatinine ratio	20 mg/g

Contrast-enhanced CT urogram of the kidneys shows no stones, masses, or cysts.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Cystoscopy
(B) Kidney biopsy
(C) Repeat urinalysis
(D) 24-Hour urine protein measurement

Item 34

A 62-year-old woman comes to the office for kidney transplantation evaluation. She has end-stage kidney disease. A peritoneal dialysis catheter was placed 2 weeks ago. She also has hypertension. Medications are amlodipine, benazepril, furosemide, metoprolol, and sodium bicarbonate.

On physical examination, vital signs are normal. A peritoneal dialysis catheter is present. The remainder of the examination is normal.

Laboratory studies:

Hepatitis B core antibody	Positive
Hepatitis B surface antibody	Positive
Hepatitis B surface antigen	Negative
Hepatitis C antibody	Positive
Hepatitis C viral load	2.8 million IU/mL

Which of the following is the most appropriate management?

(A) Avoid antiviral treatment and transplantation
(B) Begin entecavir
(C) Begin pegylated interferon and ribavirin
(D) Discuss hepatitis C virus treatment and timing

Item 35

An 87-year-old man is evaluated in the emergency department for a 36-hour history of lower abdominal discomfort, urinary frequency, and nocturia. He has no other symptoms. Medical history is significant for type 2 diabetes mellitus, hypertension, and IgG4-related autoimmune pancreatitis. Medications are metformin, hydrochlorothiazide, and rituximab. He began taking over-the-counter chlorpheniramine last week for symptoms related to seasonal allergies.

On physical examination, he is afebrile. Blood pressure is 158/64 mm Hg, and pulse rate is 78/min. There is tenderness to palpation of the lower abdomen. The prostate is diffusely enlarged.

Laboratory studies show a blood urea nitrogen level of 50 mg/dL (17.9 mmol/L) and a serum creatinine level of 2.4 mg/dL (212.2 µmol/L). Urinalysis shows a specific gravity of 1.012, 1+ blood, 1+ protein, 1+ leukocytes, 3 nondysmorphic erythrocytes/hpf, 1-3 leukocytes/hpf, and no casts.

Which of the following is the most appropriate initial step in management?

(A) Bladder ultrasonography
(B) Kidney ultrasonography
(C) MRI of the abdomen and pelvis
(D) Noncontrast CT of the abdomen and pelvis

Item 36

A 38-year-old man is evaluated during a follow-up visit for proteinuric chronic kidney disease. Family history is significant for end-stage kidney disease in two uncles and a female cousin. He has no other medical problems, and his only medication is lisinopril. The patient is of African descent.

On physical examination, vital signs are normal. There are features of generalized anasarca, with marked edema of the lower extremities. The remainder of the examination is unremarkable.

Laboratory studies:

Albumin	2.2 g/dL (22 g/L)
Total cholesterol	264 mg/dL (6.8 mmol/L)
Creatinine	1.8 mg/dL (159.1 µmol/L)
Urinalysis	No blood; 4+ protein
Urine protein-creatinine ratio	7850 mg/g

Which of the following is the most likely diagnosis?

(A) Focal segmental glomerulosclerosis
(B) Lupus nephritis
(C) Membranous nephropathy
(D) Minimal change glomerulopathy

Item 37

A 52-year-old woman is evaluated during a follow-up visit for hypertension management. She has a 10-year history of type 2 diabetes mellitus. Diabetic retinopathy was diagnosed 1 year ago. She also has obesity and hyperlipidemia. Medications are hydrochlorothiazide, metformin, empagliflozin, and atorvastatin.

On physical examination, blood pressure is 138/86 mm Hg; other vital signs are normal. BMI is 32. The remainder of the examination is unremarkable.

Laboratory studies:

Creatinine	0.9 mg/dL (79.6 µmol/L)
Electrolytes	Normal
Urine albumin-creatinine ratio	550 mg/g
Estimated glomerular filtration rate	>60 mL/min/1.73 m^2

Which of the following is the most appropriate treatment?

(A) Amlodipine
(B) Atenolol
(C) Doxazosin
(D) Losartan

Item 38

A 70-year-old woman is evaluated for right flank pain and dysuria. She has a 20-year history of type 2 diabetes mellitus with neurogenic bladder and recurrent urinary tract infections. Medications are metformin and simvastatin.

On physical examination, temperature is 38.3 °C (100.9 °F); other vital signs are normal. There is tenderness to palpation over the right flank. The remainder of the examination is normal.

Urinalysis shows cloudy urine with a specific gravity of 1.010, pH of 8.0, 1+ blood, trace protein, 3+ leukocyte esterase, and positive nitrites. Microscopic urinalysis reveals 1-2 erythrocytes/hpf, 20-25 leukocytes/hpf, and crystals (shown).

Infection with which of the following organisms is most likely?

(A) *Escherichia coli*
(B) *Proteus mirabilis*
(C) *Staphylococcus saprophyticus*
(D) *Streptococcus agalactiae*

Item 39

A 39-year-old woman is evaluated during a follow-up visit for recently diagnosed stage 2 hypertension confirmed with home blood pressure monitoring measurements taken over the past month. She also has a 12-year history of type 2 diabetes mellitus. Medications are metformin and empagliflozin.

On physical examination, blood pressure is 144/92 mm Hg, pulse rate is 88/min, and respiration rate is 18/min. BMI is 28. The remainder of the examination unremarkable.

Laboratory studies show a serum creatinine level of 0.9 mg/dL (79.6 µmol/L), normal electrolyte levels, and a urine albumin-creatinine ratio of 330 mg/g.

The patient is instructed in lifestyle modifications to control hypertension.

Which of the following is the most appropriate initial therapy?

(A) Felodipine
(B) Hydrochlorothiazide
(C) Hydrochlorothiazide and amlodipine
(D) Lisinopril

Item 40

A 38-year-old woman seeks treatment for polyuria and nocturia that began 6 weeks ago after starting lithium for bipolar disorder. Medical history is otherwise unremarkable. Her only other medication is olanzapine.

Physical examination findings, including vital signs, are normal.

Laboratory studies show a serum sodium level of 145 mEq/L (145 mmol/L) and a urine osmolality of 200 mOsm/kg H_2O.

Which of the following is the most appropriate management?

(A) Add amiloride
(B) Add furosemide
(C) Decrease water intake
(D) Increase protein intake

Item 41

A 28-year-old man is evaluated for hematuria that he noted on awakening and a 3-day history of fever, runny nose, and cough. One year ago, he had an episode of gross hematuria after running a half marathon. Evaluation at that time resulted in a biopsy diagnosis of IgA nephropathy. He has no other medical problems and takes no medications.

On physical examination, temperature is 37.9 °C (100.2 °F), and blood pressure is 110/70 mm Hg; other vital signs are normal. The nasal mucosa is edematous, with serous discharge. Examination of the oropharynx reveals erythema without exudate. There is no lymphadenopathy. Lungs are clear to auscultation. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 0.9 mg/dL (79.6 µmol/L); urinalysis shows 3+ blood, trace protein, too numerous to count erythrocytes, and no casts. Streptococcal rapid antigen test is negative.

Which of the following is the most appropriate management?

(A) Amoxicillin
(B) CT of the abdomen and pelvis
(C) Prednisone
(D) Clinical observation

Item 42

A 45-year-old man is evaluated during a routine visit in September. He has advanced chronic kidney disease due to IgA nephropathy. Medical history is also significant for chickenpox but with no history of shingles. Medications are carvedilol, diltiazem, lisinopril, and sevelamer. His vaccination history includes completion of only required childhood vaccinations and recent COVID-19 immunization.

Laboratory studies:

Hepatitis A virus IgM antibody	Negative
Hepatitis B surface antigen	Negative
Hepatitis B surface antibody	Positive
Hepatitis C virus antibody	Negative

Inactivated influenza vaccine is administered.

Which of the following is the most appropriate additional vaccine to administer at this visit?

(A) Hepatitis A vaccine
(B) Hepatitis B vaccine
(C) Herpes zoster recombinant vaccine
(D) Pneumococcal conjugate vaccine
(E) Pneumococcal polysaccharide vaccine

Item 43

H

A 66-year-old man is evaluated in the hospital for acute kidney injury following percutaneous coronary angiography and stent placement 48 hours ago. His medical history is also significant for hypertension, hyperlipidemia, type 2 diabetes mellitus, and diabetic kidney disease. Medications are lisinopril, hydrochlorothiazide, basal and prandial insulin, atorvastatin, metoprolol, clopidogrel, and aspirin.

On physical examination, blood pressure is 132/88 mm Hg, and pulse rate is 58/min without postural changes. Skin is warm and dry. The remainder of the examination is normal.

Laboratory studies:

Hematocrit	36%
Platelet count	127,000/µL (127×10^9/L)
Blood urea nitrogen	54 mg/dL (19.3 mmol/L)
Creatinine	3.6 mg/dL (318.2 µmol/L); on admission, 3.3 mg/dL (291.7 µmol/L)
Urinalysis	Specific gravity 1.010; pH 5.5; trace protein; trace leukocytes; 1-3 erythrocytes/hpf; 1-3 leukocytes/hpf; 3-5 granular casts/hpf

CONT.

Kidney ultrasound shows a 10.5-cm right kidney, 11.3-cm left kidney, and normal cortical echogenicity; there is no hydronephrosis.

Which of the following is the most likely diagnosis?

(A) Acute tubular necrosis
(B) Atheroembolic-induced acute kidney injury
(C) Hemolytic uremic syndrome
(D) Prerenal acute kidney injury

Item 44

A 45-year-old woman is evaluated in the emergency department after ingesting 50 aspirin. She is alert and reports symptoms of nausea and tinnitus. Activated charcoal is administered.

On physical examination, the patient is afebrile. Blood pressure is 130/70 mm Hg, pulse rate is 92/min, and respiration rate is 32/min. The remainder of the examination is normal.

Laboratory studies:

Creatinine	0.9 mg/dL (79.6 µmol/L)
Electrolytes:	
Sodium	139 mEq/L (139 mmol/L)
Potassium	4.0 mEq/L (4.0 mmol/L)
Chloride	91 mEq/L (91 mmol/L)
Bicarbonate	14 mEq/L (14 mmol/L)
Arterial blood gases:	
pH	7.45
P_{CO_2}	21 mm Hg (2.8 kPa)
Salicylate	65 µg/mL (470 µmol/L)

Which of the following is the most appropriate treatment?

(A) Acetazolamide
(B) Hemodialysis
(C) Intravenous 0.9% saline
(D) Intravenous sodium bicarbonate

Item 45

A 19-year-old woman is evaluated for a 2-week history of fatigue, poor appetite, arthralgia of the hands and knees, and a rash, all of which appeared 1 day after a trip to the beach. She has no other medical problems and takes no medications.

On physical examination, vital signs are normal. A malar rash characterized by pink-violet papules and plaques with sparing of the nasolabial folds is noted. The remainder of the examination, including joint examination, is normal.

Laboratory studies:

Albumin	3.1 g/dL (31 g/L)
C3	50 mg/dL (500 mg/L)
C4	9 mg/dL (90 mg/L)
Creatinine	1.1 mg/dL (97.2 µmol/L)
Antinuclear antibodies	Titer, 1:160
Urinalysis	3+ blood; 3+ protein; many erythrocytes; occasional dysmorphic erythrocytes; rare erythrocyte casts

Kidney ultrasound shows kidneys of normal size and echogenicity.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Erythrocyte sedimentation rate
(B) Extractable nuclear antigen panel
(C) Kidney biopsy
(D) Skin biopsy

Item 46

A 74-year-old woman is evaluated during a follow-up visit for hypertension and slowly progressive chronic kidney disease. She reports that she feels well and has no symptoms. Medications are atenolol, cholecalciferol, hydralazine, nifedipine, simvastatin, and sodium bicarbonate.

On physical examination, blood pressure is 130/70 mm Hg; other vital signs are normal. The remainder of the examination is unremarkable.

Laboratory studies show an estimated glomerular filtration rate of 28 mL/min/1.73 m^2.

Which of the following is the most appropriate management?

(A) Arteriovenous fistula placement evaluation
(B) Dialysis initiation
(C) Kidney transplant evaluation
(D) Renal replacement therapy education

Item 47

A 72-year-old man is evaluated for an ulcerating, painful lesion on his left calf that began as a patch of red skin 2 to 3 weeks ago. He has dialysis-dependent end-stage kidney disease, atrial fibrillation, and hypertension. Medications are amlodipine, calcium acetate, calcitriol, insulin, and warfarin. There have been no recent changes in his medications.

On physical examination, vital signs are normal. Skin findings are shown. There are no other skin changes, lesions, or rash.

Laboratory studies:

INR	2.5
Calcium	9.6 mg/dL (2.4 mmol/L)
Phosphorus	3.1 mg/dL (1.0 mmol/L)
Parathyroid hormone	361 pg/mL (361 ng/L)

A skin punch biopsy shows calcifications in the subcutaneous tissue within necrotic lipocytes and within the walls of small blood vessels. There is confluent epidermal necrosis.

Which of the following is the most likely diagnosis?

(A) Calciphylaxis
(B) Leukocytoclastic vasculitis
(C) Venous stasis ulcer
(D) Warfarin skin necrosis

Item 48

A 27-year-old woman is evaluated for hypertension. At her routine visit 6 months ago, her blood pressure was 120/76 mm Hg. There is no family history of hypertension. She has no other medical problems and takes no medications.

On physical examination, blood pressure is 146/92 mm Hg in the right arm and 148/94 mm Hg in the left arm; pulse rate is 68/min. A systolic-diastolic abdominal bruit over the right lower quadrant is heard. The remainder of the examination is unremarkable.

Laboratory studies:

Bicarbonate	24 mEq/L (24 mmol/L)
Creatinine	0.8 mg/dL (70.7 µmol/L)
Potassium	4.2 mEq/L (4.2 mmol/L)
Sodium	140 mEq/L (140 mmol/L)
Urinalysis	No blood or protein
Pregnancy test	Negative

Which of the following is the most appropriate diagnostic test to perform next?

(A) Plasma aldosterone concentration/plasma renin activity ratio
(B) Plasma fractionated metanephrines
(C) Renal artery CT angiography
(D) Urine albumin-creatinine ratio

Item 49

A 55-year-old man is evaluated for a 4-month history of persistent hyperkalemia and intermittent diarrhea. Medical history is significant for long-standing type 2 diabetes mellitus and hypertension. Medications are metformin, atorvastatin, atenolol, and amlodipine.

Physical examination findings, including vital signs, are normal.

Laboratory studies:

Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	5.3 mEq/L (5.3 mmol/L)
Chloride	112 mEq/L (112 mmol/L)
Bicarbonate	18 mEq/L (18 mmol/L)
Estimated glomerular filtration rate	56 mL/min/1.73 m^2
Urinalysis	Specific gravity 1.020; pH 5.0; no blood; no leukocytes; no ketones
Urine sodium	45 mEq/L (45 mmol/L)
Urine potassium	10 mEq/L (10 mmol/L)
Urine chloride	40 mEq/L (40 mmol/L)

Which of the following is the most likely cause of this patient's hyperkalemia?

(A) Atenolol
(B) Chronic kidney disease
(C) Diarrhea
(D) Type 1 (hypokalemic distal) renal tubular acidosis
(E) Type 4 (hyperkalemic distal) renal tubular acidosis

Item 50

A 42-year-old man is evaluated for a 4-month history of elevated blood pressure. He has attempted lifestyle modification but has been unable to lower his blood pressure. His medical history is otherwise unremarkable. The patient takes no medications. He is Black.

On physical examination, blood pressure is 148/94 mm Hg, and pulse rate is 74/min. BMI is 24. The remainder of the examination is normal.

Laboratory studies:

Creatinine	1.1 mg/dL (97.2 µmol/L)
Electrolytes	Normal
Urine albumin-creatinine ratio	Undetectable
Estimated glomerular filtration rate	>60 mL/min/1.73 m^2

A 12-lead ECG shows normal sinus rhythm, no axis, and no evidence of left ventricular hypertrophy.

In addition to continuing therapeutic lifestyle interventions, which of the following is the most appropriate treatment?

(A) Amlodipine
(B) Lisinopril
(C) Losartan
(D) Metoprolol

Item 51

H

A 45-year-old man is evaluated in the emergency department for painful myalgia of his legs and difficulty walking after running in a 10-kilometer race. Since the race, he has had minimal output of dark brown urine. He has hyperlipidemia treated with high-intensity atorvastatin.

On physical examination, temperature is 37.7 °C (99.9 °F), blood pressure is 112/67 mm Hg, and pulse rate is 88/min. Mucosae are dry, and skin turgor is diminished. The muscles of the upper and lower extremities are tender to palpation. The remainder of the examination is normal.

H CONT.

Laboratory studies:

Calcium	7.5 mg/dL (1.9 mmol/L)
Creatine kinase	57,000 U/L
Creatinine	1.5 mg/dL (132.6 µmol/L)
Electrolytes:	
Sodium	137 mEq/L (137 mmol/L)
Potassium	5.3 mEq/L (5.3 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	19 mEq/L (19 mmol/L)
Phosphorus	6.3 mg/dL (2.0 mmol/L)
Urate	9.4 mg/dL (0.55 mmol/L)
Urinalysis	Specific gravity 1.012; pH 5.5; 3+ blood; trace protein; 1-2 erythrocytes/hpf and pigmented granular casts/hpf

Which of the following is the most likely cause of this patient's findings?

(A) Immune-mediated necrotizing myopathy
(B) Inflammatory myopathy
(C) March hemoglobinuria
(D) Rhabdomyolysis

Item 52

A 46-year-old man comes to the office to discuss results of his home blood pressure monitoring. His average blood pressure measurement for the past month is 136/84 mm Hg. Based on his blood pressure measurements, previously measured lipid levels, current history of cigarette smoking, and Black race, his 10-year atherosclerotic cardiovascular disease event risk is calculated to be 10.3%. Recent laboratory studies showed his serum creatinine, blood glucose, electrolytes, and urinalysis were normal. An ECG was normal. The patient is asymptomatic and takes no medications.

On physical examination, blood pressure is 134/84 mm Hg in both arms; other vital signs are normal. BMI is 30. The remainder of the examination is normal.

The patient is instructed on the implementation of therapeutic lifestyle modifications, including weight loss, heart-healthy diet, dietary sodium restriction, exercise, and smoking cessation.

Which of the following is the most appropriate additional management?

(A) Reassess blood pressure in 3 months
(B) Start amlodipine
(C) Start chlorthalidone and losartan
(D) Start lisinopril

Item 53

A 28-year-old woman seeks preconception counseling. She has a 3-year history of primary hypertension. Medical history is otherwise unremarkable, and her only medication is ramipril.

On physical examination, blood pressure is 138/78 mm Hg. Average blood pressure with home blood pressure monitoring is 126/72 mm Hg. Other vital signs are normal. BMI is 30. The remainder of the examination is normal.

Previous evaluation revealed no evidence of retinopathy, left ventricular hypertrophy, or kidney disease.

Which of the following is the most appropriate management?

(A) Discontinue ramipril
(B) Discontinue ramipril; start hydralazine
(C) Discontinue ramipril; start spironolactone
(D) No change in therapy

Item 54

A 46-year-old man is evaluated in the emergency department for right flank and abdominal pain that began several hours ago. Medical history is significant for hypertension, type 2 diabetes mellitus, hyperlipidemia, and obesity. He has no history of kidney stones. Medications are losartan, rosuvastatin, and metformin.

On physical examination, vital signs are normal. BMI is 32. The patient appears uncomfortable. The remainder of the examination is unremarkable.

Laboratory studies:

Calcium	9.6 mg/dL (2.4 mmol/L)
Creatinine	1.4 mg/dL (123.8 µmol/L)
Electrolytes:	
Sodium	139 mEq/L (139 mmol/L)
Potassium	4.4 mEq/L (4.4 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)
Urinalysis	Specific gravity 1.018; pH 5.0; 2+ blood; no leukocyte esterase; no nitrites; 10-20 erythrocytes/hpf; 1-3 leukocytes/hpf

Noncontrast helical CT scan of the abdomen shows a 5-mm stone at the right ureteropelvic junction. Hounsfield units are compatible with a uric acid stone.

Which of the following is the most appropriate treatment?

(A) Allopurinol
(B) Lithotripsy
(C) Potassium citrate
(D) Tamsulosin

Item 55

A 49-year-old woman is evaluated during a routine follow-up visit. Medical history is significant for chronic kidney disease, hypertension, and HIV infection. She has been taking her current antihypertensive medications for 6 years. Her antiretroviral regimen was changed 6 weeks ago to a more convenient once-daily dosing regimen. Current medications are dolutegravir-abacavir-lamivudine and lisinopril-hydrochlorothiazide.

Findings on physical examination, including vital signs, are normal.

Laboratory studies performed 2 weeks ago showed a continued suppressed viral load and a serum creatinine level increase from her baseline of 1.2 mg/dL to 1.6 mg/dL (106.1-141.4 µmol/L).

Today's laboratory studies:

Creatinine	1.6 mg/dL (141.4 µmol/L)
Urinalysis	No blood, protein, or erythrocytes
Urine albumin-creatinine ratio	100 mg/g (unchanged from baseline)

Which of the following is the most appropriate management?

(A) Discontinue lisinopril-hydrochlorothiazide
(B) Measure 24-hour urine creatinine clearance
(C) Return to prior antiretroviral regimen
(D) No further management is indicated

Item 56

A 44-year-old woman is evaluated during a follow-up visit for chronic hypertension. Over the past month, her average blood pressure measured with home blood pressure monitoring was 150/90 mm Hg. There is no family history of hypertension. She has no other medical problems. The patient adheres to a low sodium diet. Medications are maximum doses of amlodipine, atenolol, and lisinopril.

On physical examination, blood pressure is 150/96 mm Hg, and pulse rate is 64/min; other vital signs are normal. BMI is 26. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 0.8 mg/dL (70.7 µmol/L) and normal electrolyte levels. Urinalysis shows no blood, protein, or leukocyte esterase.

Which of the following is the most appropriate next step in management?

(A) Add chlorthalidone
(B) Measure plasma aldosterone concentration/plasma renin activity ratio
(C) Measure plasma fractionated metanephrines
(D) Obtain renal artery imaging

Item 57

A 54-year-old woman is evaluated in the hospital for polyuria 3 days after undergoing resection of a glioblastoma multiforme. She is receiving 0.45% saline at 50 mL/h and nasogastric enteral nutrition because of difficulty swallowing. Medications are dexamethasone and levetiracetam.

On physical examination, she is in no acute distress. Vital signs are normal. Muscle strength is 4/5 in her left upper extremity. The remainder of the examination is normal.

Laboratory studies:

Blood urea nitrogen	85 mg/dL (30.3 mmol/L)
Creatinine	1.4 mg/dL (123.8 µmol/L)
Electrolytes:	
Sodium	152 mEq/L (152 mmol/L)
Potassium	3.8 mEq/L (3.8 mmol/L)
Chloride	118 mEq/L (118 mmol/L)
Bicarbonate	23 mEq/L (23 mmol/L)
Glucose	170 mg/dL (9.4 mmol/L)
Urine sodium	32 mEq/L (32 mmol/L)
Urine potassium	24 mEq/L (24 mmol/L)
Urine osmolality	560 mOsm/kg H_2O

Which of the following is the most likely cause of this patient's hypernatremia?

(A) Diabetes insipidus
(B) Electrolyte diuresis
(C) Glucose diuresis
(D) Urea diuresis

Item 58

A 61-year-old man is evaluated for bilateral action tremor of the hands and rarely the feet that began 7 days ago. The intensity of the tremor varies and is worse in the morning and late afternoon. He has no other symptoms. There is no family history of tremor or Parkinson disease. Four months ago, he underwent living-donor related kidney transplantation. Medical history is also significant for hypertension. Medications are atorvastatin, lisinopril, metoprolol, mycophenolate mofetil, nifedipine, prednisone, sulfamethoxazole-trimethoprim, tacrolimus, and valganciclovir.

On physical examination, vital signs are normal. There is bilateral tremor of the hands present when the hands are resting in the lap, with outstretched arms, and with various actions. The remainder of the examination is normal.

Laboratory studies show a serum creatinine level of 1.2 mg/dL (106.1 µmol/L).

Which of the following is the most likely medication responsible for this patient's tremor?

(A) Metoprolol
(B) Mycophenolate mofetil
(C) Prednisone
(D) Tacrolimus

Item 59

A 63-year-old man is evaluated in the hospital for acute kidney injury following a motor vehicle accident 48 hours ago. He sustained pelvic and rib fractures and a splenic laceration requiring splenectomy. He received isotonic fluids (17 L) plus norepinephrine for blood pressure support. He is intubated and on mechanical ventilation. During the past 24 hours, urine output fluctuated from 10 to 15 mL/h, with a 24-hour urine output of 280 mL. Medications are vancomycin, ceftazidime, intravenous norepinephrine, and 150 mL/h of intravenous crystalloid fluids.

On physical examination, the patient is mechanically ventilated and sedated. Temperature is 38.3 °C (100.9 °F), blood pressure is 88/52 mm Hg, pulse rate is 96/min, and respiration rate is 16/min. Oxygen saturation is 95% with the patient breathing 0.40 F_{IO_2}. Jugular venous pressure is elevated. Cardiac examination is normal, and lungs are clear to auscultation. The abdomen is distended and tense. A bladder catheter is draining small amounts of urine.

Laboratory studies:

Hemoglobin	8.5 g/dL (85 g/L)
Blood urea nitrogen	73 mg/dL (26.1 mmol/L)
Creatinine	3.6 mg/dL (318.2 µmol/L)
Urinalysis	Specific gravity 1.012; pH 5.5; 1+ blood; no protein; 1-3 erythrocytes/hpf; scattered hyaline casts

H CONT.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bladder pressure measurement
(B) CT urography
(C) Kidney biopsy
(D) Kidney ultrasonography

Item 60

A 46-year-old man is evaluated in the hospital for hypernatremia. He was hospitalized 2 days ago with hyperglycemic hyperosmolar syndrome. He was obtunded and intubated to protect his airway. He was treated with 3 liters of 0.9% saline and insulin infusion. Medical history is significant for type 2 diabetes mellitus treated with metformin.

On hospital day 2, blood pressure is 155/96 mm Hg, and pulse rate is 76/min. Other vital signs and the remainder of the examination are normal.

The patient is extubated but his level of consciousness fluctuates and he cannot follow commands or eat or drink fluids without choking.

Current laboratory studies:

Electrolytes:	
Sodium	152 mEq/L (152 mmol/L)
Potassium	3.2 mEq/L (3.2 mmol/L)
Chloride	124 mEq/L (124 mmol/L)
Bicarbonate	19 mEq/L (19 mmol/L)
Glucose	200 mg/dL (11.1 mmol/L)

Which of the following is the most appropriate treatment for this patient's hypernatremia?

(A) Intravenous 5% dextrose
(B) Intravenous 0.45% saline
(C) Intravenous 0.9% saline
(D) Water via nasogastric tube

Item 61

A 62-year-old woman is evaluated during a follow-up visit for hypertension and chronic kidney disease. Medical history is otherwise unremarkable. Medications are losartan and amlodipine. The patient is adherent to her medication regimen and low sodium diet.

On physical examination, blood pressure is 148/94 mm Hg in both arms, pulse rate is 65/min, and respiration rate is 18/min. BMI is 30. Neck examination shows jugular venous distension. Cardiac examination reveals an S_4 gallop. Lungs are clear to auscultation. There is 1+ pitting edema over the pretibial lower extremities and ankles bilaterally. The remainder of the examination is unremarkable.

Laboratory studies:

Bicarbonate	22 mEq/L (22 mmol/L)
Creatinine	2.6 mg/dL (229.8 µmol/L)
Potassium	4.9 mEq/L (4.9 mmol/L)
Sodium	136 mEq/L (136 mmol/L)
Urine albumin-creatinine ratio	1500 mg/g
Estimated glomerular filtration rate	24 mL/min/1.73 m^2

Which of the following is the most appropriate additional treatment?

(A) Carvedilol
(B) Furosemide
(C) Hydralazine
(D) Lisinopril

Item 62

H

A 36-year-old woman is evaluated during a routine follow-up visit for stage G4 chronic kidney disease. Her estimated glomerular filtration rate is 22 mL/min/1.73 m^2. Medications are lisinopril, sevelamer, and sodium bicarbonate. She has selected hemodialysis for her renal replacement therapy, and an arteriovenous fistula will eventually be placed in her nondominant left arm.

Three weeks later, the patient is hospitalized with septic shock secondary to community-acquired pneumonia. Venous access for the administration of fluids, vasopressors, and antibiotics is urgently needed.

Which of the following is most appropriate method of venous access for this patient?

(A) Internal jugular vein insertion of a central venous catheter
(B) Peripherally inserted central catheter in the left arm
(C) Peripherally inserted central catheter in the right arm
(D) Subclavian vein insertion of a central venous catheter

Item 63

A 25-year-old man is evaluated in the emergency department for a 1-week history of fatigue, dyspnea, and hemoptysis. He has no other medical problems and takes no medications.

On physical examination, blood pressure is 155/95 mm Hg, and respiration rate is 25/min; other vital signs are normal. No rash is noted. The remainder of the examination is unremarkable.

Laboratory studies:

C3	95 mg/dL (950 mg/L)
C4	20 mg/dL (200 mg/L)
Creatinine	2.3 mg/dL (203.3 µmol/L)
Antinuclear antibodies	Negative
Antimyeloperoxidase antibodies	Negative
Antiproteinase-3 antibodies	Negative
Urinalysis	3+ blood; 3+ protein; numerous erythrocytes and erythrocyte casts

Kidney biopsy shows necrotizing and crescentic glomerulonephritis with linear staining for IgG on immunofluorescence.

Which of the following is the most appropriate serologic test to perform next?

(A) Anti-double-stranded DNA antibodies
(B) Anti-glomerular basement membrane antibodies
(C) Anti-phospholipase A2 receptor antibodies
(D) Circulating IgA levels

Item 64

A 73-year-old man is evaluated during a follow-up visit for an unexplained worsening of chronic kidney disease. Recent laboratory studies showed a serum creatinine level of 2.4 mg/dL (212.2 µmol/L); 9 months ago, serum creatinine was 1.1 mg/dL (97.2 µmol/L). He has had two episodes of idiopathic acute pancreatitis in the past 3 years.

The physical examination, including vital signs, is normal.

Laboratory studies:

Creatinine	2.4 mg/dL (212.2 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	5.3 mEq/L (5.3 mmol/L)
Chloride	108 mEq/L (108 mmol/L)
Bicarbonate	20 mEq/L (20 mmol/L)
Urinalysis	Specific gravity 1.020; pH 5.0; no blood; 1+ protein; 1+ glucose; no leukocyte esterase; 0-2 erythrocytes/hpf; 3-5 leukocytes/hpf; moderate granular casts

Kidney ultrasound shows a 12-cm right kidney and a 13-cm left kidney with a mild increase in cortical echogenicity.

Kidney biopsy shows chronic tubulointerstitial nephritis with dense lymphoplasmacytic infiltrates.

Which of the following is the most likely diagnosis?

(A) IgG4-related disease
(B) Sarcoidosis
(C) Systemic lupus erythematosus
(D) Tubulointerstitial nephritis with uveitis

Item 65

A 65-year-old man is evaluated for a 7-week history of increasing fatigue and poor appetite. Medical history is otherwise unremarkable. He takes no medications.

Physical examination findings, including vital signs, are normal.

Laboratory studies:

Hematocrit	28%
Albumin	3.0 g/dL (30 g/L)
Calcium	10.4 mg/dL (2.6 mmol/L)
Creatinine	1.6 mg/dL (141.4 µmol/L)
Electrolytes:	
Sodium	130 mEq/L (130 mmol/L)
Potassium	3.6 mEq/L (3.6 mmol/L)
Chloride	99 mEq/L (99 mmol/L)
Bicarbonate	23 mEq/L (23 mmol/L)
Osmolality	290 mOsm/kg H_2O
Total protein	9.8 g/dL (98 g/L)
Urine osmolality	240 mOsm/kg H_2O
Urine sodium	45 mEq/L (45 mmol/L)

Which of the following is the most likely cause of this patient's hyponatremia?

(A) Hypercalcemia
(B) Multiple myeloma
(C) Poor solute intake
(D) Psychogenic polydipsia
(E) Syndrome of inappropriate antidiuretic hormone secretion

Item 66

A 25-year-old woman is evaluated in the emergency department for weakness and muscle cramps. During the past 3 months, she had a weight loss of 15 kg (33.1 lb). She has no other medical problems and takes no medications.

On physical examination, blood pressure is 124/72 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. BMI is 36. Muscle strength is 4/5 in the upper and lower extremities. Other than weakness, the remainder of the neurologic examination is normal.

Laboratory studies:

Creatinine	0.8 mg/dL (70.7 µmol/L)
Electrolytes:	
Sodium	135 mEq/L (135 mmol/L)
Potassium	2.4 mEq/L (2.4 mmol/L)
Chloride	79 mEq/L (79 mmol/L)
Bicarbonate	44 mEq/L (44 mmol/L)
Arterial blood gases:	
pH	7.61
P_{CO_2}	45 mm Hg (6.0 kPa)
Urine chloride	3 mEq/L (3 mmol/L)

Which of the following is the most likely diagnosis?

(A) Bartter syndrome
(B) Cushing syndrome
(C) Primary hyperaldosteronism
(D) Surreptitious vomiting

Item 67

A 37-year-old man is hospitalized for a 2-month history of anorexia, 4.5-kg (10-lb) weight loss, nocturia, morning nausea, and fatigue. He has no other medical problems and takes no medications.

On physical examination, blood pressure is 197/98 mm Hg, pulse rate is 80/min, and respiration rate is 18/min. BMI is 24. Funduscopic examination reveals hypertensive retinopathy. There is no papilledema. Cardiac examination reveals a sustained apical impulse and an S_4. The lungs are clear to auscultation. There is 1+ edema of the lower extremities.

Laboratory studies:

Blood urea nitrogen	163 mg/dL (58.2 mmol/L)
Creatinine	14.2 mg/dL (1255.3 µmol/L)
Electrolytes:	
Sodium	134 mEq/L (134 mmol/L)
Potassium	4.9 mEq/L (4.9 mmol/L)
Chloride	103 mEq/L (103 mmol/L)
Bicarbonate	11 mEq/L (11 mmol/L)
Urinalysis	Specific gravity 1.010; pH 7; 1+ blood; 1+ protein; 2-5 erythrocytes/hpf; 1-3 leukocytes/hpf; scattered granular and hyaline casts

H CONT.

Kidney ultrasound shows a 7.3-cm right kidney and a 7.7-cm left kidney; there is marked cortical echogenicity and loss of corticomedullary distinction but no hydronephrosis.

Which of the following is the most appropriate management?

(A) Dialysis
(B) Intravenous 0.9% saline
(C) Intravenous methylprednisolone
(D) Percutaneous kidney biopsy

Item 68

A 52-year-old woman is evaluated during a follow-up visit for hypertension. Losartan and chlorthalidone were started 1 month ago. She adheres to her medication regimen and low sodium diet. She has no other medical problems and takes no other medications. Previous ECG and results of a comprehensive metabolic profile and urinalysis were normal.

On physical examination, blood pressure is 145/82 mm Hg, and pulse rate is 70/min; other vital signs are normal. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 0.8 mg/dL (70.7 µmol/L) and a serum potassium level of 3.6 mEq/L (3.6 mmol/L).

Which of the following is the most appropriate additional treatment?

(A) Aliskiren
(B) Amlodipine
(C) Hydralazine
(D) Hydrochlorothiazide

Item 69

A 26-year-old woman is evaluated in the emergency department for acute flank pain and gross hematuria.

On physical examination, the patient is afebrile. Pulse rate is 102/min; other vital signs are normal. Costovertebral angle tenderness is noted. The abdomen is soft and nontender.

Urinalysis shows 3+ blood, trace protein, no nitrites or leukocyte esterase, 2-3 leukocytes/hpf, and too numerous to count erythrocytes. Pregnancy test is positive.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Abdominal MRI
(B) Kidney ultrasonography
(C) Kidney, ureter, and bladder plain radiography
(D) Noncontrast helical abdominal CT
(E) Ureteroscopy

H

Item 70

A 17-year-old boy is evaluated in the hospital for acute kidney injury. He was hospitalized 24 hours ago for a bone marrow biopsy, which confirmed the presence of acute lymphoblastic leukemia. On admission, blood urea nitrogen level was 24 mg/dL (8.6 mmol/L) and serum creatinine level was 1.0 mg/dL (88.4 µmol/L). Intravenous 0.9% saline was started at 125 mL/h. This morning, his serum creatinine level is 1.9 mg/dL (168 µmol/L). His urine output diminished to less than 50 mL/h.

On physical examination, vital signs are normal. There are few scattered ecchymoses on the upper and lower extremities. The remainder of the examination is normal.

Laboratory studies (hospital day 2):

Blood urea nitrogen	46 mg/dL (16.4 mmol/L)
Calcium	6.3 mg/dL (1.6 mmol/L)
Creatinine	1.9 mg/dL (168 µmol/L)
Electrolytes:	
Sodium	137 mEq/L (137 mmol/L)
Potassium	6.1 mEq/L (6.1 mmol/L)
Chloride	103 mEq/L (103 mmol/L)
Bicarbonate	17 mEq/L (17 mmol/L)
Phosphorus	9.6 mg/dL (3.1 mmol/L)
Urate	15.2 mg/dL (0.90 mmol/L)
Urinalysis	Specific gravity 1.010; pH 5.0; 1+ blood; trace protein; multiple uric acid crystals, scattered granular casts and hyaline casts

Intravenous 0.9% saline is increased to 200 mL/h.

Which of the following is the most appropriate additional treatment?

(A) Allopurinol
(B) Febuxostat
(C) Rasburicase
(D) Urinary alkalinization

Item 71

A 24-year-old man is evaluated in the emergency department for a 3-hour history of right flank pain that radiates to the groin. He reports nausea and dysuria but no fever or chills. Medical history is otherwise unremarkable. He takes no medications. Intravenous ketorolac is initiated for pain.

On physical examination, pulse rate is 104/min; other vital signs are normal. The patient appears uncomfortable. Abdominal examination reveals right costovertebral tenderness. The remainder of the examination is normal.

Laboratory studies show a serum calcium level of 9.8 mg/dL (2.5 mmol/L) and a serum creatinine level of 0.8 mg/dL (70.7 µmol/L). Urinalysis shows a specific gravity of 1.020; a pH of 5.0; 1+ blood; no leukocyte esterase; no nitrites; 20-30 erythrocytes/hpf; and 0-1 leukocytes/hpf.

Which of the following is the most sensitive imaging test to perform?

(A) Intravenous pyelography
(B) Kidney and bladder ultrasonography
(C) Kidney, ureter, and bladder radiography
(D) Noncontrast helical abdomen and pelvis CT

Item 72

A 65-year-old man is evaluated during a follow-up visit for stage G4 chronic kidney disease. He has a reduced appetite but no other significant symptoms. Four months ago, anemia was discovered and confirmed to be related to his chronic kidney disease. Medical history is also significant for hypertension and type 2 diabetes mellitus. Medications are atenolol, atorvastatin, basal insulin, prandial insulin, metolazone, sevelamer, furosemide, hydralazine, and nifedipine.

On physical examination, vital signs are normal. There is a mature arteriovenous fistula with a thrill. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin	10.1 g/dL (101 g/L)
Creatinine	3.3 mg/dL (291.7 µmol/L)
Potassium	4.2 mEq/L (4.2 mmol/L)
Bicarbonate	19 mEq/L (19 mmol/L)
Estimated glomerular filtration rate	20 mL/min/1.73 m^2

Which of the following is the most appropriate treatment?

(A) Erythropoietin-stimulating agent
(B) Hemodialysis
(C) High-protein diet
(D) Sodium bicarbonate supplement

Item 73

A 35-year-old woman is evaluated during a follow-up visit for recurrent microscopic hematuria without proteinuria. Family history is significant for microscopic hematuria in her brother and mother; her two other siblings have no urinary abnormalities. There is no family history of chronic kidney disease or end-stage kidney disease. Her medical history is otherwise unremarkable, and she takes no medications.

Physical examination findings, including vital signs, are normal.

Laboratory studies show a serum creatinine level of 0.7 mg/dL (61.9 µmol/L); urinalysis shows 2+ blood, no protein, and 20-30 erythrocytes/hpf.

Kidney ultrasound shows normal-sized kidneys with no masses or stones.

Which of the following is the most likely diagnosis?

(A) Autosomal dominant tubulointerstitial kidney disease
(B) Fabry disease
(C) Hereditary nephritis (Alport syndrome)
(D) Thin glomerular basement membrane disease

Item 74

A 70-year-old woman is evaluated during a follow-up visit. One month ago, lisinopril was initiated for confirmed hypertension. Pretreatment blood pressure was 152/78 mm Hg. Therapeutic lifestyle interventions and pharmacologic therapies were initiated. Medical history is also significant for peripheral vascular disease, hyperlipidemia, and type 2 diabetes mellitus. Other medications are glipizide, rosuvastatin, and low-dose aspirin. She lives independently in her own home.

On physical examination, blood pressure is 144/69 mm Hg, and pulse rate is 86/min. Cardiovascular examination reveals an S_4 and diminished lower extremity pulses. There is no peripheral edema. The remainder of the examination is normal.

Laboratory studies:

Creatinine	1.4 mg/dL (123.8 µmol/L)
Potassium	4.4 mEq/L (4.4 mmol/L)
Estimated glomerular filtration rate	34 mL/min/1.73 m^2
Urine albumin-creatinine ratio	15 mg/g

Which of the following is the most appropriate management?

(A) Add chlorthalidone
(B) Add prazosin
(C) Switch lisinopril to ramipril
(D) Continue current medical therapy

Item 75

A 48-year-old man is evaluated in the emergency department for sudden onset of dyspnea. He has a 2-week history of progressive leg edema and bilateral flank pain. He has no other medical problems and takes no medications.

On physical examination, respiratory rate is 26/min; other vital signs are normal. There is 2-mm pitting edema in the lower extremities to the mid-shin bilaterally. The remainder of the examination is unremarkable.

Laboratory studies:

Albumin	2.0 g/dL (20 g/L)
Total cholesterol	401 mg/dL (10.4 mmol/L)
Complement levels	Normal
Creatinine	1.1 mg/dL (97.2 µmol/L)
Antinuclear antibodies	Negative
Urinalysis	No blood; 4+ protein; 0-1 erythrocytes/hpf; 0-1 leukocytes/hpf
Urine protein-creatinine ratio	8900 mg/g

Hepatitis B and C, HIV, and syphilis testing results are negative.

CT of the chest shows segmental pulmonary embolism. CT of the abdomen and pelvis shows bilateral renal vein thromboses.

Low-molecular-weight heparin is initiated.

Which of the following is the most appropriate diagnostic test to perform next?

(A) ANCA antibodies
(B) Anti-double-stranded DNA antibodies
(C) Anti-phospholipase A2 receptor antibodies
(D) Kidney biopsy following discontinuation of heparin

Item 76

A 58-year-old woman is evaluated during a follow-up visit for progressive stage G3 chronic kidney disease. Her average blood pressure using home blood pressure monitoring is 130/70 mm Hg. She walks three times weekly for exercise. Medical history is also significant for hypertension. Medications are chlorthalidone, cholecalciferol, furosemide, losartan, and metoprolol.

On physical examination, vital signs are normal. There is no jugular venous distension. Lungs are clear to auscultation. There is trace bilateral leg edema.

Laboratory studies:

Total cholesterol	178 mg/dL (4.61 mmol/L)
Creatinine	1.5 mg/dL (132.6 µmol/L)
Estimated glomerular filtration rate	44 mL/min/1.73 m^2
Urine albumin-creatinine ratio	420 mg/g

Which of the following is the most likely expected cause of premature death in this patient?

(A) Cardiovascular disease
(B) End-stage kidney disease
(C) Infection
(D) Renal cell carcinoma

Item 77

A 62-year-old man is evaluated in the emergency department for increasing abdominal and bilateral flank pain. The pain began yesterday, 2 days after he took primaquine prescribed as antimalarial prophylaxis for planned travel.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 102/55 mm Hg, pulse rate is 110/min, and respiration rate is 22/min. Cardiac examination reveals tachycardia without extra sounds. There is no edema. The remainder of the examination is unremarkable.

Laboratory studies:

Haptoglobin	10 mg/dL (100 mg/L)
Hemoglobin	7.9 g/dL (79 g/L)
Reticulocyte count	8%
Total bilirubin	5.8 mg/dL (99.2 µmol/L)
Blood urea nitrogen	32 mg/dL (11.4 mmol/L)
Creatinine	1.9 mg/dL (168 µmol/L)
Lactate dehydrogenase	1250 U/L
Urinalysis	Specific gravity 1.010; pH 5.0; 3+ heme; 1+ albumin; no erythrocytes, leukocytes, or leukocyte esterase; numerous pigmented granular casts

Examination of peripheral blood smear shows bite cells.

Which of the following is the most likely diagnosis?

(A) Acute interstitial nephritis
(B) Heme pigment nephropathy
(C) Prerenal acute kidney injury
(D) Rhabdomyolysis

Item 78

A 28-year-old woman is evaluated for leg weakness and mild nausea several days after treatment with intravenous ferric carboxymaltose for severe iron deficiency anemia. She has Crohn disease. She reports that her appetite is good. Medications are prednisone, sulfasalazine, infliximab, calcium carbonate, and vitamin D.

On physical examination, temperature is 37.0 °C (98.6 °F), pulse rate is 80/min, and respiration rate is 16/min. BMI is 18. Abdominal examination reveals tenderness. Motor strength is 4/5 in the hip flexors and extensors. The remainder of the examination is normal.

Laboratory studies:

Electrolytes:	
Sodium	136 mEq/L (136 mmol/L)
Potassium	3.8 mEq/L (3.8 mmol/L)
Chloride	108 mEq/L (108 mmol/L)
Bicarbonate	21 mEq/L (21 mmol/L)
Phosphorus	1.2 mg/dL (0.39 mmol/L)
Fractional excretion of phosphorus	21%

Which of the following is the most likely cause of this patient's hypophosphatemia?

(A) Ferric carboxymaltose
(B) Low phosphorus diet
(C) Metabolic acidosis
(D) Prednisone

Item 79

A 67-year-old man is evaluated during a follow-up visit for resistant hypertension. He was recently evaluated for primary hyperaldosteronism, and the screening plasma aldosterone concentration/plasma renin activity ratio was >20. A dedicated adrenal CT scan showed diffuse bilateral adrenal hyperplasia. The patient also has type 2 diabetes mellitus, hyperlipidemia, coronary artery disease, and activity-limiting COPD. He does not want surgery under any circumstances. Medications are rosuvastatin, metformin, canagliflozin, amlodipine, enalapril, metoprolol, chlorthalidone, low-dose aspirin, albuterol, and tiotropium.

On physical examination, blood pressure is 160/94 mm Hg in both arms, pulse rate is 76/min, and respiration rate is 18/min. BMI is 24. Cardiac examination is notable for an S_4. Pulmonary examination reveals occasional expiratory wheezing.

Which of the following is the most appropriate next step in management?

(A) Bilateral adrenal vein sampling
(B) Eplerenone therapy
(C) MRI of the adrenal glands
(D) Oral sodium loading test

Item 80

A 45-year-old woman is evaluated in the emergency department for altered mental status.

H CONT.

On physical examination, the patient is tachypneic and obtunded. Temperature is normal, blood pressure is 94/64 mm Hg, pulse rate is 80/min, and respiration rate is 24/min.

Laboratory studies:

Electrolytes:	
Sodium	133 mEq/L (133 mmol/L)
Potassium	3.9 mEq/L (3.9 mmol/L)
Chloride	110 mEq/L (110 mmol/L)
Bicarbonate	16 mEq/L (16 mmol/L)
Arterial blood gases:	
pH	7.4
P_{CO_2}	27 mm Hg (3.6 kPa)

Which of the following is the most likely acid-base disorder?

(A) Respiratory alkalosis and increased anion gap metabolic acidosis
(B) Respiratory alkalosis and normal anion gap metabolic acidosis
(C) Respiratory alkalosis, normal gap metabolic acidosis, and metabolic alkalosis
(D) Respiratory alkalosis with chronic compensation

Item 81

A 31-year-old woman is evaluated for lower extremity edema, a rash over both legs, and fatigue that have worsened during the past 3 months. She has no other medical problems and takes no medications. The patient was born in Egypt and moved to the United States at 20 years of age.

On physical examination, the patient is afebrile, and blood pressure is 147/96 mm Hg. There is 1-mm pitting edema through the mid-shins bilaterally.

The rash is shown.

Laboratory studies:

Albumin	3.9 g/dL (39 g/L)
C3	58 mg/dL (580 mg/L)
C4	5.0 mg/dL (50 mg/L)
Creatinine	2.6 mg/dL (229.8 µmol/L)
Cryoglobulins	Positive
Rheumatoid factor	Positive
Urinalysis	3+ blood; 3+ protein; erythrocytes and rare erythrocyte casts
Urine protein-creatinine ratio	2100 mg/g

A kidney biopsy is scheduled.

Which of the following viral studies will support the most likely diagnosis?

(A) Fourth-generation HIV testing
(B) Hepatitis A virus antibody testing
(C) Hepatitis B virus surface antigen and surface antibody testing
(D) Hepatitis C virus antibody testing

Item 82

A 57-year-old man is evaluated during a follow-up visit after beginning hydrochlorothiazide 1 month ago. He has hypertension and chronic kidney disease. He has no other medical problems. Medications are lisinopril, 40 mg once daily; amlodipine, 10 mg once daily; and hydrochlorothiazide, 25 mg once daily. The patient maintains a low sodium diet.

On physical examination, blood pressure is 138/86 mm Hg; other vital signs are normal. There is 1+ pitting pretibial edema bilaterally. The remainder of the examination is normal.

Laboratory studies:

Bicarbonate	22 mEq/L (22 mmol/L)
Creatinine	2.5 mg/dL (221 µmol/L)
Potassium	5.4 mEq/L (5.4 mmol/L)
Sodium	135 mEq/L (135 mmol/L)
Estimated glomerular filtration rate	28 mL/min/1.73 m^2
Urine protein-creatinine ratio	1800 mg/g

Which of the following is the most appropriate treatment?

(A) Discontinue hydrochlorothiazide; begin eplerenone
(B) Discontinue hydrochlorothiazide; begin furosemide
(C) Increase hydrochlorothiazide dose
(D) Continue current management

Item 83

A 59-year-old man is evaluated for recently discovered normochromic, normocytic anemia and an elevated serum creatinine level. He is otherwise well and takes no medications.

All physical examination findings, including vital signs and neurologic examination, are normal.

Laboratory studies:

Hemoglobin	9.2 g/dL (92 g/L)
Creatinine	3.0 mg/dL (265.2 µmol/L); 1 year ago: 1.0 mg/dL (88.4 µmol/L)
Urinalysis	Trace protein; no blood, erythrocytes, leukocytes, leukocyte esterase, or nitrites
Urine protein-creatinine ratio	2500 mg/g

Which of the following is the most appropriate test to perform next?

(A) Repeat urinalysis
(B) 24-Hour urine collection for total protein
(C) Sulfosalicylic acid test
(D) Urine albumin-creatinine ratio
(E) Urine protein electrophoresis

Item 84

A 52-year-old man is evaluated for a 3-day history of diffuse muscle aches. He has type 2 diabetes mellitus, hypertension, and stage G3 chronic kidney disease. Medications are metformin, valsartan, atorvastatin, calcium, and vitamin D.

On physical examination, vital signs are normal. There is significant tenderness over the thighs and arms. The remainder of the examination is normal.

Laboratory studies:

Calcium	8.4 mg/dL (2.1 mmol/L)
Creatine kinase	16,200 U/L
Creatinine	1.8 mg/dL (159.1 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	5.2 mEq/L (5.2 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	18 mEq/L (18 mmol/L)
Phosphorus	6.1 mg/dL (2.0 mmol/L)

Which of the following is the most likely cause of this patient's hyperphosphatemia?

(A) Chronic kidney disease
(B) Insulin deficiency
(C) Rhabdomyolysis
(D) Vitamin D

Item 85

A 54-year-old man is evaluated for the nephrotic syndrome 10 days after undergoing a kidney biopsy. He reports normal urine volume and no hematuria. He has noticed mild bilateral flank aches during the past 2 days. Prebiopsy serum creatinine level was 0.9 mg/dL (79.6 µmol/L). Medical history is also significant for hyperlipidemia. Medications are furosemide and atorvastatin.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 148/88 mm Hg, and pulse rate is 72/min. Bilateral costovertebral angle tenderness is noted. There is 2+ lower extremity edema. The remainder of the examination is normal.

Laboratory studies show a serum creatinine level of 3.2 mg/dL (282.9 µmol/L). Urinalysis shows a specific gravity of 1.012; pH of 5.0; 3+ blood; 3+ protein; 1+ leukocytes; >100 erythrocytes/hpf; occasional leukocytes; and no casts.

Kidney biopsy shows membranous nephropathy with minimal interstitial fibrosis and no glomerulosclerosis.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Anti–phospholipase receptor A2 antibody measurement
(B) Fractional excretion of sodium
(C) Radionuclide imaging
(D) Renal ultrasonography with Doppler

Item 86

A 27-year-old man is evaluated in the ICU for septic shock. For the past 3 months, he has received dialysis for end-stage kidney disease with a tunneled catheter because his arteriovenous fistula has not matured for use. He reports a 1-day history of fever and malaise.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 90/50 mm Hg, pulse rate is 89/min, and respiration rate is 22/min. A right internal jugular tunneled hemodialysis catheter is in place with no erythema or discharge at the exit site. A normal-appearing and functioning left arteriovenous fistula is present. The remainder of the examination is normal.

Blood and urine cultures are obtained.

Cefepime and vancomycin are initiated, repeated fluid boluses are administered, and intravenous norepinephrine is started.

Which of the following is the most appropriate additional management?

(A) Antibiotic lock therapy
(B) Arteriovenous fistula excision
(C) Exchange the tunneled catheter
(D) Remove the tunneled catheter

Item 87

A 24-year-old woman is evaluated during a follow-up visit for hypokalemia. She has occasional muscle cramps but no weakness, polyuria, or diarrhea. Medical history is unremarkable. Family history is unobtainable. She takes no medications.

On physical examination, blood pressure is 98/68 mm Hg. Other vital signs and the remainder of the examination are normal.

Laboratory studies:

Calcium	10.2 mg/dL (2.55 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	3.1 mEq/L (3.1 mmol/L)
Chloride	100 mEq/L (100 mmol/L)
Bicarbonate	29 mEq/L (29 mmol/L)
Magnesium	1.4 mg/dL (0.58 mmol/L)
Urine sodium	48 mEq/L (48 mmol/L)
Urine potassium	32 mEq/L (32 mmol/L)
Urine chloride	54 mEq/L (54 mmol/L)
Urine diuretic screen	Negative
Spot urine calcium-creatinine ratio	Low

Which of the following is the most likely diagnosis?

(A) Gitelman syndrome
(B) Laxative abuse
(C) Primary hyperaldosteronism
(D) Surreptitious vomiting

Item 88

A 45-year-old man is evaluated during a routine follow-up visit for stage G3 chronic kidney disease. He also has hypertension and type 2 diabetes mellitus. Medications are cholecalciferol, hydrochlorothiazide, metformin, canagliflozin, and valsartan.

On physical examination, blood pressure is 140/80 mm Hg; other vital signs are normal. The remainder of the examination is normal.

His calculated 10-year risk of an atherosclerotic cardiovascular disease event is 7.5%.

Laboratory studies:

Total cholesterol	186 mg/dL (4.8 mmol/L)
HDL cholesterol	34 mg/dL (0.88 mmol/L)
LDL cholesterol	113 mg/dL (2.9 mmol/L)
Creatinine	2.0 mg/dL (176.8 µmol/L)
Estimated glomerular filtration rate	47 mL/min/1.73 m^2

Which of the following is the most appropriate treatment to reduce this patient's risk for atherosclerotic cardiovascular disease?

(A) Evolocumab
(B) Ezetimibe
(C) High-intensity rosuvastatin
(D) Moderate-intensity atorvastatin

Item 89

A 33-year-old woman is evaluated in the hospital following a recent diagnosis of membranoproliferative glomerulonephritis. She engages in transactional sex. She has no other medical problems and takes no medications.

On physical examination, blood pressure is 142/90 mm Hg; other vital signs are normal. There is 1-mm pitting edema of the ankles bilaterally. The remainder of the examination is unremarkable.

Laboratory studies:

C3	69 mg/dL (690 mg/L)
C4	5 mg/dL (50 mg/L)
Creatinine	2.5 mg/dL (221 µmol/L)
Antinuclear antibodies	Negative
Antimyeloperoxidase antibodies	Negative
Antiproteinase-3 antibodies	Negative
Fourth-generation HIV test	Negative
Urinalysis	3+ blood; 2+ protein
Urine protein-creatinine ratio	1700 mg/g

Kidney biopsy showed membranoproliferative glomerulonephritis with positive immunofluorescence staining for IgG, IgM, C1q, and C3.

Which of the following is the most likely cause of this patient's glomerulonephritis?

(A) Genetic mutations of alternative complement pathway proteins
(B) Hepatitis B virus infection
(C) Hepatitis C virus infection
(D) Syphilis

Item 90

A 44-year-old woman is evaluated in the emergency department for confusion. Previous history is unknown.

On physical examination, vital signs are normal. She is oriented to her name only. Pulmonary and cardiovascular examinations are normal. The patient has confusion, but the neurologic examination is otherwise unremarkable.

Laboratory studies:

Electrolytes:	
Sodium	118 mEq/L (118 mmol/L)
Potassium	3.1 mEq/L (3.1 mmol/L)
Chloride	90 mEq/L (90 mmol/L)
Bicarbonate	22 mEq/L (22 mmol/L)
Osmolality	248 mOsm/kg H_2O

Which of the following is the most appropriate treatment?

(A) Fluid restriction
(B) 0.9% saline
(C) 3% saline plus desmopressin
(D) Tolvaptan

Item 91

A 41-year-old woman is evaluated during a follow-up visit for stage 2 hypertension confirmed by daytime ambulatory blood pressure monitoring. She also has a 10-year history of type 2 diabetes mellitus and hyperlipidemia. Medications are atorvastatin, metformin, and empagliflozin.

On physical examination, blood pressure is 142/92 mm Hg, and pulse rate is 72/min; other vital signs are normal. BMI is 28. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 0.9 mg/dL (79.6 µmol/L). Urine dipstick reveals no blood or protein.

The patient is instructed in lifestyle modifications for blood pressure control.

Which of the following is the most appropriate additional management?

(A) Begin amlodipine
(B) Begin hydrochlorothiazide
(C) Continue nonpharmacologic therapy with blood pressure measurement in 3 months
(D) Obtain urine albumin-creatinine ratio

Item 92

A 52-year-old woman is evaluated in the emergency department for abdominal pain and metabolic acidosis. The patient has been drinking alcohol steadily for 1 week and has been brought to the emergency department by friends. The patient also had episodes of nausea and vomiting and abdominal pain over the past 24 to 48 hours. The patient was hospitalized 1 year ago with isopropyl alcohol intoxication. She reports no other medical problems and takes no medications.

On physical examination, blood pressure is 110/72 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. BMI is 18. Abdominal examination reveals diffuse tenderness to palpation. The remainder of the examination is normal.

Laboratory studies:

Blood urea nitrogen	32 mg/ dL (11.4 mmol/L)
Electrolytes:	
Sodium	139 mEq/L (139 mmol/L)
Potassium	3.9 mEq/L (3.9 mmol/L)
Chloride	100 mEq/L (100 mmol/L)
Bicarbonate	11 mEq/L (11 mmol/L)

H CONT.

Ethanol	40 mg/dL (8.64 mmol/L)
Glucose	72 mg/dL (4.0 mmol/L)
Plasma osmolality	290 mOsm/kg H_2O
Urinalysis	Specific gravity 1.030; pH 5.5; no blood; trace ketones

Which of the following is the most likely diagnosis?

(A) Alcoholic ketoacidosis
(B) Ethylene glycol toxicity
(C) Isopropyl alcohol toxicity
(D) Methanol toxicity

Item 93

A 32-year-old man is evaluated during a follow-up visit after passing his third calcium oxalate kidney stone in 4 years despite maintaining a high urine volume. He has no other medical problems. His only medication is potassium citrate, which was initiated after passing the most recent stone. He drinks 4 cups of coffee daily and typically eats meals at fast-food restaurants.

Physical examination findings, including vital signs, are normal.

Laboratory studies:
24-Hour urine studies:

Volume	2600 mL
pH	6.5
Calcium	295 mg (normal range, 50-300 mg)
Citrate	850 mg (normal range, 100-300 mg)
Oxalate	35 mg (normal range, 10-40 mg)
Uric acid	640 mg (normal range, 250-750 mg)

The patient is counseled to start a low sodium diet.

Which of the following is the most appropriate additional management?

(A) Decrease calcium intake
(B) Decrease coffee intake
(C) Decrease oxalate intake
(D) Start allopurinol
(E) Start chlorthalidone

Item 94

An 84-year-old woman is evaluated during a follow-up visit for stage G4 chronic kidney disease. Her only symptom is lack of energy. She is independent in her activities of daily living. She has declined renal replacement therapy after attending a dialysis education class. She understands the process and purpose of dialysis and the consequence of non-treatment but prefers non-dialytic therapy. Medical history is also significant for diabetes mellitus, heart failure, hypertension, and stroke. Medications are furosemide, lisinopril, hydralazine, insulin aspart, insulin detemir, nifedipine, metoprolol, and aspirin, 81 mg.

On physical examination, blood pressure is 160/72 mm Hg, and pulse rate is 60/min; other vital signs are normal. Cardiac examination reveals an S_4. The remainder of the examination is noncontributory.

Laboratory studies:

Calcium	9.4 mg/dL (2.4 mmol/L)
Creatinine	2.3 mg/dL (203.3 µmol/L)
Potassium	4.7 mEq/L (4.7 mmol/L)
Phosphorus	4.4 mg/dL (1.4 mmol/L)
Estimated glomerular filtration rate	26 mL/min/1.73 m^2

Which of the following is the most appropriate management?

(A) Add a phosphate binder
(B) Discontinue all medications except insulin
(C) Intensify hypertension management
(D) Refer for hospice care

Item 95

A 32-year-old woman is seen following evaluation for a single episode of painless hematuria that she noted last week. She has chronic kidney disease secondary to chronic tubulointerstitial nephritis confirmed by biopsy. She took Chinese herbal weight loss pills daily for 3 years. She took acetaminophen or ibuprofen for arthralgia three or four times monthly for 5 years. Since the kidney biopsy, she has discontinued all drugs and supplements. She has no other medical problems.

The physical examination, including vital signs, is normal.

Urinalysis shows a specific gravity of 1.012, 3+ blood, 1+ protein, 1+ leukocytes, 25-50 nondysmorphic erythrocytes/hpf, 3-5 leukocytes/hpf, and no casts; urine culture is negative.

CT scan of the abdomen and pelvis shows normal kidneys and collecting system.

Which of the following is the most appropriate management?

(A) Cystoscopy with retrograde pyelography
(B) MRI of the kidneys
(C) Renal angiography
(D) Observation

Item 96

H

A 69-year-old man is evaluated 7 days after starting nafcillin to treat a culture-proven methicillin-sensitive *Staphylococcal aureus* sternal wound infection. The infection was diagnosed 10 days after coronary artery bypass surgery. History is significant for diabetes mellitus. Other medications are aspirin, metformin, metoprolol, atorvastatin, and acetaminophen as needed.

On physical examination, vital signs are normal. The sternal wound appears to be healing, with minimal tenderness and redness and decreased drainage. The remainder of the examination is unremarkable.

H CONT.

Laboratory studies:

C3	61 mg/dL (610 mg/L)
C4	13 mg/dL (130 mg/L)
Creatinine	2.0 mg/dL (176.8 µmol/L); before hospital admission: 0.9 mg/dL (79.6 µmol/L)
Urinalysis	3+ blood; 2+ protein; 30–40 erythrocytes/hpf; 2–5 leukocytes/hpf; dysmorphic erythrocytes; rare erythrocyte casts

Kidney biopsy shows a mild proliferative glomerulonephritis with infiltrating neutrophils, granular C3, and IgG and IgM staining on immunofluorescence; hump-shaped subepithelial electron-dense deposits are seen on electron microscopy.

Which of the following is the most appropriate treatment?

(A) Add lisinopril
(B) Add prednisone
(C) Continue nafcillin
(D) Initiate sodium restriction and furosemide

Item 97

A 37-year-old woman is evaluated for a new-onset headache. She describes the headache as a steady pain located in the front of her head, bilaterally, and not associated with any other symptoms. The headache has been present for more than 24 hours. She is in the third trimester of her first pregnancy. Until now, her pregnancy has been unremarkable and she has otherwise been healthy.

On physical examination, blood pressure is 145/95 mm Hg; other vital signs are normal. There is no papilledema. On abdominal examination, the patient has a gravid uterus consistent with her stage of pregnancy, and there is no abdominal tenderness. Neurologic examination is normal.

Laboratory studies:

Hemoglobin	12.3 g/dL (123 g/L)
Platelet count	156,000/µL (156 × 10^9/L)
Alanine aminotransferase	Normal
Aspartate aminotransferase	Normal
Creatinine	1.4 mg/dL (123.8 µmol/L)
Random urine protein-creatinine ratio	125 mg/g

Which of the following is the most likely diagnosis?

(A) Acute fatty liver of pregnancy
(B) Migraine headache
(C) Pheochromocytoma
(D) Preeclampsia

Item 98

A 26-year-old man is referred for an elevated serum creatinine level of 1.4 mg/dL (123.8 µmol/L) that was measured when he presented to an urgent care center for flank pain. The flank pain was determined to be musculoskeletal and caused by a weight-lifting injury. A subsequent urinalysis was normal, and a random urine albumin-creatinine ratio was 10 mg/g. He reports that he takes no creatine supplements but is evasive when questioned about anabolic steroid use. His medical history is otherwise unremarkable, and he takes no prescribed medications.

On physical examination, vital signs are normal. BMI is 29. The patient is muscular, with no evidence of subcutaneous fat. He has mild muscle tenderness in the right lower back. The remainder of the examination is unremarkable.

Which of the following is the most appropriate test to perform next?

(A) Blood urea nitrogen measurement
(B) Creatinine clearance
(C) Radionuclide imaging
(D) Serum cystatin C measurement

Item 99

A 67-year-old man is evaluated during a follow-up visit 4 weeks after being diagnosed with the nephrotic syndrome. He has a 7-year history of well-controlled type 2 diabetes mellitus with no retinopathy, neuropathy, or clinically evident vascular disease. He has no other medical problems, and his only medication is metformin.

On physical examination, blood pressure is 110/60 mm Hg; other vital signs are normal. No rash is noted. There is 2-mm pitting edema in the lower extremities to the knees bilaterally.

Laboratory studies:

Albumin	2.1 g/dL (21 g/L)
Total cholesterol	330 mg/dL (8.5 mmol/L)
Creatinine	1.4 mg/dL (123.8 µmol/L) (4 months ago, 1.0 mg/dL [88.4 µmol/L])
Hemoglobin A_{1c}	6.9%
Serum protein electrophoresis	Negative
24-Hour urine protein excretion	12,000 mg/24 h

Kidney biopsy shows expansion of the mesangial areas by deposits of homogenous, pale eosinophilic material that are positive with Congo red staining and demonstrate apple-green birefringence when viewed under polarized light.

Which of the following is the most likely diagnosis?

(A) Diabetic kidney disease
(B) IgA nephropathy
(C) Membranous nephropathy
(D) Renal AL amyloidosis

Item 100

An 81-year-old woman is evaluated in the emergency department for abrupt onset of lower extremity edema that began 2 weeks ago and has progressed to generalized edema. Medical history is significant for hypertension. Her only medication is amlodipine.

On physical examination, vital signs are normal. There is periorbital edema, ascites, and pitting edema of the forearms and lower extremities to the thighs. The remainder of the examination, including cardiovascular and pulmonary examinations, is unremarkable.

Laboratory studies:

Albumin	1.6 g/dL (16 g/L)
Total cholesterol	364 mg/dL (9.4 mmol/L)
Creatinine	2.8 mg/dL (248 µmol/L); 2 months ago: 0.7 mg/dL (61.9 µmol/L)
Urinalysis	No blood; 4+ protein

Kidney ultrasound with Doppler shows normal-sized echogenic kidneys with no hydronephrosis; there are no abnormalities on Doppler flow.

Which of the following is the most likely diagnosis?

(A) ANCA-associated glomerulonephritis
(B) Anti-glomerular basement membrane antibody disease
(C) Membranous nephropathy
(D) Minimal change glomerulopathy

Item 101

An 87-year-old man is hospitalized for the inability to void. He has a 4-year history of urinary hesitancy and dribbling. He lives alone with the assistance of a nephew but finds it increasingly difficult to live independently. He has no other medical history and takes no medications.

On physical examination, he is thin and frail appearing. Blood pressure is 158/64 mm Hg, and pulse rate is 78/min without orthostatic changes. BMI is 22. The prostate is diffusely enlarged. There is 1+ lower extremity edema. Generalized weakness is noted. The remainder of the examination is unremarkable.

A bladder catheter drains 850 mL of urine.

Laboratory studies show a blood urea nitrogen level of 133 mg/dL (47.5 mmol/L) and a serum creatinine level of 8.9 mg/dL (786.8 µmol/L).

Kidney ultrasound shows an 8.3-cm right kidney and a 7.9-cm left kidney, marked cortical echogenicity and thinning, and moderate-severe hydronephrosis.

During the first 24 hours, urine output with the bladder catheter in place is 1240 mL. Follow-up bladder ultrasound shows less than 50 mL of residual urine. On hospital day 2 the urine output is 340 mL.

On hospital day 3, the serum creatinine level is 8.2 mg/dL (724.8 µmol/L). Repeat kidney ultrasound shows persistent hydronephrosis.

Which of the following is the most appropriate next step in management?

(A) Discuss goals of care
(B) Initiate intravenous 0.9% saline
(C) Obtain noncontrast CT of abdomen and pelvis
(D) Place bilateral ureteral stents

Item 102

A 31-year-old woman is evaluated during a follow-up visit for progressive autosomal dominant polycystic kidney disease. She has a recent history of an infected kidney cyst. She also has hypertension. Family history is significant for end-stage kidney disease in her father at 50 years of age due to autosomal dominant polycystic kidney disease. Her only medication is lisinopril.

On physical examination, vital signs are normal. Abdominal examination reveals a palpable kidney on the right side. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 1.3 mg/dL (114.9 µmol/L), representing a decrease in estimated glomerular filtration rate of >5 mL/min/1.73 m^2 from 1 year ago. Liver chemistry tests are normal.

Which of the following is the most appropriate management?

(A) Discontinue lisinopril; start telmisartan
(B) Obtain ultrasonography of the kidneys
(C) Start octreotide
(D) Start tolvaptan

Item 103

A 45-year-old woman is evaluated during a follow-up visit for newly diagnosed severe hypertension. She began low-dose hydrochlorothiazide and amlodipine therapy 1 month ago. There is no family history of hypertension. She has no other medical problems and takes no other medications.

On physical examination, blood pressure is 164/100 mm Hg in both arms, pulse rate is 76/min, and respiration rate is 18/min. BMI is 24. The remainder of the examination is normal.

Laboratory studies:

Bicarbonate	30 mEq/L (30 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)
Potassium	2.9 mEq/L (2.9 mmol/L)
Sodium	138 mEq/L (138 mmol/L)
Urinalysis	No blood or protein

Which of the following is the most appropriate diagnostic test to perform next?

(A) Plasma aldosterone concentration/plasma renin activity ratio
(B) Plasma fractionated metanephrines measurement
(C) Renal artery CT angiography
(D) 24-Hour urine free cortisol measurement

Item 104

A 23-year-old woman is evaluated during a follow-up visit for focal segmental glomerulosclerosis that was diagnosed 3 weeks ago. The edema in her lower extremities has not improved on her current regimen of prednisone, losartan, atorvastatin, and maximal doses of oral furosemide.

On physical examination, vital signs are normal. The patient weighs 72 kg (158.7 lb). There is 3-mm pitting edema of the lower extremities through the mid-thigh, equal on both sides. The remainder of the examination is unremarkable.

Laboratory studies:

Albumin	2.0 g/dL (20 g/L)
Total cholesterol	303 mg/dL (7.8 mmol/L)
Creatinine	0.6 mg/dL (53 µmol/L)
Urine protein-creatinine ratio	9150 mg/g

CT of the chest is normal.

Which of the following is the most appropriate management?

(A) Add metolazone
(B) Administer furosemide by continuous intravenous infusion
(C) Administer furosemide by intravenous bolus
(D) Discontinue prednisone; add cyclosporine
(E) Hemodialysis with ultrafiltration

Item 105

A 33-year-old man is evaluated for acute kidney injury 48 hours after being hospitalized for herpes simplex virus encephalitis. Diagnosis was confirmed with polymerase chain reaction testing of the cerebrospinal fluid. He is being treated with intravenous high-dose acyclovir. Empiric therapy with ceftriaxone plus vancomycin was initiated and then discontinued after the results of the cerebrospinal fluid analysis became available. Medical history is significant for chronic kidney disease due to hereditary nephritis and hypertension. Outpatient medications are lisinopril and hydrochlorothiazide, both held since admission.

On physical examination, vital signs are normal. The patient has some difficulty with attention and orientation to time but is otherwise neurologically intact. The remainder of the examination is normal.

Current laboratory studies:

Creatinine	2.3 mg/dL (203.3 µmol/L); baseline: 1.8 mg/dL (159.1 µmol/L)
Electrolytes:	
Sodium	137 mEq/L (137 mmol/L)
Potassium	5.6 mEq/L (5.6 mmol/L)
Chloride	102 mEq/L (102 mmol/L)
Bicarbonate	26 mEq/L (26 mmol/L)
Urinalysis	Specific gravity 1.010; pH 7.5; 1+ blood; 2+ protein; 1+ leukocytes; 1-3 leukocytes/hpf; 3-5 erythrocytes/hpf; fine-needle crystals

Kidney ultrasound shows an 11-cm right kidney and an 11.8-cm left kidney with normal cortical appearance and without hydronephrosis.

Which of the following is the most likely cause of this patient's acute kidney injury?

(A) Acute glomerulonephritis
(B) Acute interstitial nephritis
(C) Acute tubular necrosis
(D) Intratubular obstruction

Item 106

A 46-year-old woman is evaluated during a follow-up visit for hypertension, type 2 diabetes mellitus, and stage G3 chronic kidney disease. She reports no symptoms. Medications are losartan, amlodipine, metformin, canagliflozin, and rosuvastatin.

On physical examination, blood pressure is 124/72 mm Hg. Other vital signs and the remainder of the examination are unremarkable.

Laboratory studies:

Creatinine	1.6 mg/dL (141.4 µmol/L)
Electrolytes:	
Sodium	136 mEq/L (136 mmol/L)
Potassium	5.6 mEq/L (5.5 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)
Urine albumin-creatinine ratio	320 mg/g

ECG is normal.

The patient is counseled to start a low potassium diet.

Which of the following is the most appropriate management?

(A) Add hydrochlorothiazide
(B) Add patiromer
(C) Administer intravenous calcium gluconate
(D) No further treatment

Item 107

A 31-year-old woman seeks preconception counseling. She has systemic lupus erythematosus and lupus nephritis, both of which have been stable for the past year; she has had no proteinuria for more than 12 months. She currently feels well. Medications are mycophenolate mofetil, hydroxychloroquine, and low-dose prednisone.

Physical examination findings, including vital signs, are normal.

Which of the following medications should be discontinued in this patient before conception?

(A) Hydroxychloroquine
(B) Mycophenolate mofetil
(C) Prednisone
(D) No change in medication is required

Item 108

A 60-year-old woman is evaluated during a follow-up visit for stage G3 proteinuric chronic kidney disease due to type 2 diabetes mellitus. Medications are lisinopril and metformin.

On physical examination, blood pressure is 137/80 mm Hg, and pulse rate is 83/min; other vital signs are normal. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin A_{1c}	8.3%
Creatinine	1.3 mg/dL (114.9 µmol/L)
Potassium	4.3 mEq/L (4.3 mmol/L)
Estimated glomerular filtration rate	45 mL/min/1.73 m^2
Spot urine protein-creatinine ratio	3680 mg/g

Which of the following is the most appropriate additional treatment?

(A) Canagliflozin
(B) Glyburide
(C) Losartan
(D) Pioglitazone
(E) Sitagliptin

Answers and Critiques

Item 1 Answer: A

Educational Objective: Diagnose β_2-agonist–related hypokalemia.

The most likely cause of this patient's hypokalemia is albuterol (**Option A**). Hypokalemia is defined as a serum potassium level <3.5 mEq/L (3.5 mmol/L). It can be divided into disorders of internal balance (movement of potassium between the intracellular and extracellular compartments) and disorders of external balance (potassium intake and output). β_2-Agonists such as albuterol that are administered intravenously or by inhalation increase the activity of the Na^+/K^+-ATPase, which drives potassium into cells. This causes a transient decline in the extracellular potassium concentration. The decline in serum potassium is dose dependent and related to the potency of the drug, averaging approximately 0.5 mEq/L (0.5 mmol/L) but can be much greater. In patients with underlying heart disease, the rapid decline in serum potassium can cause fatal arrhythmias. When significant hypokalemia is secondary to acute transcellular shifts, such as in this case, total body potassium is normal and excessive potassium replacement may cause rebound hyperkalemia.

Similar to β_2-agonists, insulin increases Na^+/K^+-ATPase activity and will acutely lower the extracellular potassium concentration. This effect of insulin on potassium homeostasis is separate from its effect on glucose metabolism. In this patient, however, it is unlikely that his hyperglycemia with a serum glucose level of 124 mg/dL (6.9 mmol/L) is high enough (**Option B**) to stimulate significant insulin release to cause hypokalemia.

Blockage of the cellular potassium channel by the divalent cation barium can cause acute decreases in serum potassium. Although magnesium is a divalent cation, it does not affect the potassium channel in cell membranes, and thus hypermagnesemia (**Option C**) cannot cause hypokalemia.

Although prednisone (**Option D**) has mineralocorticoid activity, any mineralocorticoid increase in potassium excretion would not occur rapidly and would therefore not explain this patient's hypokalemia. In addition, hyperaldosteronism is associated with hypertension and a metabolic alkalosis.

Respiratory disturbances have minimal effect on potassium distribution, and thus respiratory alkalosis (**Option E**) would not be expected to cause a significant decrease in potassium in this patient.

KEY POINTS

- β_2-Agonists can cause hypokalemia by facilitating intercellular shifts of potassium.
- When hypokalemia is secondary to acute transcellular shifts, total body potassium is normal and potassium replacement may cause rebound hyperkalemia.

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Item 2 Answer: C

Educational Objective: Prevent contrast-associated nephropathy.

The most appropriate periprocedure measure to prevent contrast-associated nephropathy (CAN) is to administer intravenous 0.9% saline pre- and postprocedure (**Option C**) for this patient undergoing cardiac catheterization. Multiple patient-related risk factors have been associated with CAN. The primary risk factor is a reduced estimated glomerular filtration rate (eGFR). Some studies find an added risk of CAN from diabetes mellitus. Well-established additional risk factors include nephrotoxic agents and exposures, hypotension, hypovolemia, albuminuria, and impaired kidney perfusion (e.g., as occurs in heart failure). Although multiple myeloma has historically been considered a risk factor for CAN, this is not supported by more recent literature. A 2020 guideline from the American College of Radiology and the National Kidney Foundation recommends that the risk for CAN be determined primarily by using the chronic kidney disease stage and associated eGFR measurement. Patients at highest risk for CAN include those with recent acute kidney injury and those with an eGFR <30 mL/min/1.73 m^2. Prophylaxis with intravenous 0.9% saline pre- and postprocedure is indicated for patients not undergoing dialysis who have an eGFR <30 mL/min/1.73 m^2 or acute kidney injury. In individual high-risk circumstances, prophylaxis may be considered in patients with eGFR of 30 to 44 mL/min/1.73 m^2 at the discretion of the ordering clinician. Prophylaxis is not indicated for patients with stable eGFR ≥45 mL/min/1.73 m^2. The presence of a solitary kidney should not independently influence decision-making regarding the risk for CAN.

Renal replacement therapy should neither be initiated nor have a schedule adjustment solely based on contrast media administration. Postprocedure initiation of hemodialysis (**Option A**) directed at removal of contrast from the blood has been attempted in a few small studies with mixed results.

Neither infusion of sodium bicarbonate pre- and postprocedure (**Option B**) nor use of oral N-acetylcysteine (**Option D**) is recommended to prevent CAN due to a lack of consistent evidence demonstrating efficacy.

KEY POINTS

- Contrast-associated nephropathy prophylaxis with intravenous 0.9% saline pre- and postprocedure is indicated for patients who have an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or acute kidney injury.

(Continued)

KEY POINTS *(continued)*

- Contrast-associated nephropathy prophylaxis is not indicated for patients with a stable estimated glomerular filtration rate ≥45 mL/min/1.73 m^2.

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Item 3 Answer: C

Educational Objective: Screen for malignancy in an older patient with membranous nephropathy.

A noncontrast CT of the chest (**Option C**) should be performed to screen for lung cancer in this patient newly diagnosed with phospholipase A2 receptor (PLA2R)-negative membranous nephropathy (MN) and a history of heavy tobacco use. Testing for PLA2R antigen is used to help distinguish primary from secondary forms of MN. This distinction is crucial because secondary (PLA2R antigen-negative) forms are expected to remit if the underlying systemic disease responsible for the lesion is successfully treated. Therefore, age- and sex-appropriate cancer screening is recommended for all patients at the time of diagnosis, even those with PLA2R positivity. Thus, the initial step in management of newly diagnosed MN is to evaluate for secondary forms of the disease, which account for approximately 25% of MN cases and include lupus-, hepatitis-, drug-, and malignancy-associated forms of MN. Cancer screening is particularly important in evaluating for secondary forms of MN in patients >65 years of age. Up to 25% of such patients will have a malignancy discovered within 1 year of diagnosis. This 69-year-old man with a 45-pack-year history of smoking has not undergone risk factor–appropriate cancer screening, which would include a noncontrast CT of the chest.

Renal vein thrombosis is found in up to 20% of patients with MN. Doppler ultrasonography screening for renal vein thrombosis (**Option A**) is reserved for when acute kidney injury, flank pain, and/or gross hematuria raise suspicion for this complication.

MN is associated with a higher risk for clotting when serum albumin is <2.8 g/dL (28 g/L); this patient's serum albumin is 2.9 g/dL (29 g/L). The symmetric lower extremity edema in this patient is more consistent with the nephrotic syndrome than a lower extremity clot; therefore, Doppler ultrasonography of his legs (**Option B**) would not be required.

Random (spot) urine protein-creatinine ratio (**Option D**), particularly when collected on first morning void, can serve as a surrogate for 24-hour urine protein quantification. This test is unnecessary in this case, as the more accurate quantification of proteinuria via 24-hour urine protein excretion has already been performed.

KEY POINTS

- The initial step in the management of newly diagnosed membranous nephropathy (MN) is to evaluate for secondary forms of the disease, and cancer screening is particularly important in evaluating for secondary forms of MN in patients >65 years of age.
- Testing for phospholipase A2 receptor (PLA2R) antigen is used to help distinguish primary (PLA2R antigen-positive) from secondary (PLA2R antigen-negative) forms of membranous nephropathy.

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Item 4 Answer: C

Educational Objective: Manage a patient following initiation of a renin-angiotensin system inhibitor.

The most appropriate treatment for this patient is to discontinue lisinopril and add furosemide (**Option C**). Treatment of hypertension with a renin-angiotensin system inhibitor, such as an ACE inhibitor (e.g., lisinopril) or an angiotensin receptor blocker (ARB) (e.g., losartan), is indicated in patients with stage G3 chronic kidney disease (CKD) or higher or for those with stage G1 or G2 CKD with albuminuria (urine albumin-creatinine ratio ≥300 mg/g). However, kidney function and serum potassium levels should be reassessed 2 to 3 weeks after initiation of an ACE inhibitor or ARB. A 25% to 30% increase in serum creatinine is acceptable, but the dose may need to be lowered or the medication discontinued if a more severe decline in kidney function is observed, such as in this patient. A decrease of the glomerular filtration rate of this magnitude is usually the result of renovascular hypertension. In patients with significant hyperkalemia, a loop diuretic such as furosemide can be added to promote kaliuresis.

Continuing lisinopril, with or without the addition of furosemide (**Options A, B**), or replacing lisinopril with losartan (**Option D**), places the patient at increased risk for progressive kidney injury and hyperkalemia. However, discontinuation of lisinopril in this case is a temporary solution. This patient's laboratory tests can be repeated in 2 to 3 weeks after the discontinuation of lisinopril and addition of furosemide. If the laboratory tests have normalized, reinitiation of lisinopril at a lower dose can be considered with careful monitoring of serum creatinine and potassium levels.

KEY POINTS

- In patients with chronic kidney disease, kidney function and serum potassium levels should be reassessed 2 to 3 weeks after initiation of an ACE inhibitor or angiotensin receptor blocker.
- Following initiation of an ACE inhibitor or angiotensin receptor blocker, a >30% increase in serum creatinine levels necessitates decreasing the dose of or discontinuing these agents.

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Item 5 Answer: A

Educational Objective: Screen for renal cell carcinoma in a patient with acquired cystic kidney disease.

The most appropriate management of this patient's acquired kidney cysts is annual kidney ultrasonography (**Option A**). Patients with end-stage kidney disease (ESKD) are at increased risk for renal cell carcinoma compared with the general population. Acquired cystic changes of the kidney are common in patients with severe chronic kidney disease (CKD) and ESKD and are at risk for malignant transformation. Risk factors for acquired cystic kidney disease include longer duration of ESKD and dialysis and male sex. For patients with ESKD and acquired kidney cysts, decisions about screening must be individualized based on the competing issues of risk for renal cell carcinoma versus a shortened overall life expectancy. This young patient is a kidney transplant candidate with extended life expectancy. His kidney ultrasound confirms the presence of acquired cysts, a few of which are complex with internal septations; however, there is no evidence of malignant change with no solid components or neovascularization. This patient should have annual ultrasonography of the kidneys to monitor for malignant conversion and undergo nephrectomy if a suspicious mass develops.

Preemptive nephrectomy (**Option B**) is an invasive intervention that would put this patient at risk for surgical complications with no clear benefit; he has no evidence of renal cell carcinoma or other indications for nephrectomy, such as recurrent infections related to the kidney.

Tolvaptan (**Option C**) has been FDA approved for treatment of patients with autosomal dominant polycystic kidney disease. However, there is no role for tolvaptan in patients with acquired kidney cysts.

For older patients with ESKD and those who are not transplant candidates, screening is not recommended (**Option D**), even in the presence of known acquired cystic kidney disease. The American Society of Nephrology's Choosing Wisely Campaign recommends not screening for malignancy in patients with reduced life expectancy. However, because of the increased risk for renal cell carcinoma in this patient population, development of symptoms or signs consistent with renal cell carcinoma should be investigated. For example, spontaneous improvement in hemoglobin is suspicious for renal cell carcinoma–related erythropoietin production.

KEY POINTS

- Patients with end-stage kidney disease are at increased risk for renal cell carcinoma.

(Continued)

KEY POINTS *(continued)*

- Screening for renal cell carcinoma in patients with end-stage kidney disease and acquired cystic kidney disease may be reasonable in patients with a longer life expectancy.

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Item 6 Answer: A

Educational Objective: Treat myeloma cast nephropathy.

The most appropriate treatment is chemotherapy (**Option A**). This patient presents with acute kidney injury (AKI), anemia, hypercalcemia, and a biopsy confirming the presence of myeloma cast nephropathy. Myeloma cast nephropathy is caused by the interaction and aggregation of filtered free light chains and Tamm-Horsfall protein causing intratubular obstruction and damage. Rapid lowering of free light chains with bortezomib-based chemotherapy with high-dose dexamethasone correlates with kidney recovery and is more effective than plasmapheresis or hemodialysis.

In this patient with preserved urine output, hemodialysis (**Option B**) with either a high-cutoff or regular dialyzer would not be recommended. Extended high-cutoff hemodialysis uses a high-cutoff dialyzer with very large membrane pores and high permeability to immunoglobulin light chains to remove free light chains. This high-cutoff hemodialysis has proven better than conventional hemodialysis in lowering light chain burden, but in a randomized trial of patients with myeloma cast nephropathy treated with a bortezomib-based chemotherapy regimen, the use of high-cutoff hemodialysis did not result in improved kidney survival compared with conventional hemodialysis. These data suggest that the use of chemotherapy is the most important factor in reduction of light chain burden. Fluid overload, hyperkalemia, and uremia remain indications for hemodialysis in all patients with AKI.

Hospice referral (**Option C**) is premature for this patient. Nearly 50% of all patients with multiple myeloma develop kidney disease, most commonly AKI caused by cast nephropathy, and this complication does lead to reduced 1-year survival rates. However, advances in chemotherapy regimens are improving both mortality rates and kidney survival rates, and this patient with a normal functional status and no comorbidities would benefit from chemotherapy.

Small trials initially showed that therapeutic plasmapheresis (**Option D**) improved renal outcomes in myeloma cast nephropathy, but a large randomized trial of therapeutic plasmapheresis failed to show benefit. If used, plasmapheresis is combined with chemotherapy to reduce the rate of light chain production rather than as monotherapy.

KEY POINT

- Initiation of chemotherapy is the most appropriate treatment for myeloma cast nephropathy and is aimed at reducing the concentration of free light chains.

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Item 7 Answer: D

Educational Objective: Identify hypercoagulability as a complication of the nephrotic syndrome.

The most likely complication to develop in this patient during the next 12 months is venous thromboembolism (VTE) (**Option D**). The nephrotic syndrome is a hypercoagulable state due to urinary losses of anticoagulant proteins (antithrombin III, protein S) and fibrinolytics as well as hepatic overproduction of procoagulant proteins (factor V, factor VIII, fibrinogen). A very low serum albumin level seems to be a surrogate measure for abnormalities in antithrombin and fibrinogen. As a result, patients with the nephrotic syndrome are at increased risk for lower extremity, pulmonary, and renal vein thrombosis. Clots are most often seen in patients with membranous nephropathy, such as this patient, in which VTE risk appears to begin at a serum albumin level <2.8 g/dL (28 g/L) and increases proportionately with declining albumin levels. Therefore, any patient with nephrotic-range proteinuria and significant hypoalbuminemia (typically <2.5 g/dL [25 g/L]) should be considered at risk. Most VTE events occur in the first 6 months after a diagnosis of the nephrotic syndrome is made. Prophylactic anticoagulation of asymptomatic patients with the nephrotic syndrome and hypoalbuminemia is controversial, and no randomized clinical trials are available to help guide clinical decision-making.

Diabetes mellitus (**Option A**) is the most common cause of the nephrotic syndrome. Other causes of the nephrotic syndrome do not predispose the development of diabetes mellitus, independent of the role that glucocorticoid therapy may play in predisposing a patient to hyperglycemia.

Approximately one third of patients with membranous nephropathy achieve spontaneous remission in the first year following diagnosis. Of those who do not achieve remission, 75% will respond to immunosuppression with glucocorticoids plus alkylator agents, calcineurin inhibitors, or rituximab. Progression to end-stage kidney disease (**Option B**) requiring dialysis is unlikely, especially in the first year of the diagnosis.

Pulmonary hemorrhage (**Option C**) is a complication associated with glomerulonephritis caused by anti-glomerular basement membrane antibody disease or possibly with ANCA-associated glomerulonephritis; however, it is not expected in a patient with membranous nephropathy.

KEY POINTS

- Patients with the nephrotic syndrome and hypoalbuminemia are at increased risk for venous thromboembolism (VTE); VTE is most often seen in patients with membranous nephropathy.
- Prophylactic anticoagulation of asymptomatic patients with the nephrotic syndrome and hypoalbuminemia is controversial.

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Item 8 Answer: A

Educational Objective: Evaluate progressive kidney disease.

The most appropriate management is kidney biopsy (**Option A**) for this patient with a significant decline in kidney function. In addition, this patient has unexplained moderately increased albuminuria and an increase in echogenicity on kidney ultrasound, suggesting a chronic condition. Clinical and laboratory features are often insufficient for definitive diagnosis of kidney disease. Therefore, kidney biopsy may be essential for diagnosis and management. Indications include glomerular hematuria, severely increased albuminuria, acute or chronic kidney disease of unclear cause, and kidney transplant dysfunction or monitoring. In this case, the patient has an elevated serum creatinine level with albuminuria and possible chronic kidney disease without a clear cause. Although further urine and serologic testing will be performed to guide diagnosis, a kidney biopsy will provide definitive diagnosis.

The patient has moderately increased albuminuria (albumin-creatinine ratio of 30-300 mg/g). The urine protein-creatinine ratio will be greater than the urine albumin-creatinine ratio due to the presence of nonalbumin protein and therefore will be in the pathologic range. Therefore, random urine protein-creatinine ratio (**Option B**) will not add new information in this case.

Because the patient has a significant loss of kidney function, a reassessment of serum creatinine in 3 months (**Option C**) would not be appropriate and would result in potentially harmful delay in the diagnosis of a treatable disease.

Discontinuation of lisinopril for hydrochlorothiazide (**Option D**) is not indicated. Due to preferential dilation of the efferent arteriole, the ACE inhibitor lisinopril may reduce glomerular filtration rate and increase serum creatinine; however, this change in serum creatinine will occur within days of drug initiation and then will stabilize. In this case, the serum creatinine increased without a change in dose, suggesting that lisinopril is not the cause of the rising serum creatinine and will not be resolved by discontinuing the drug. In addition, treatment with lisinopril cannot account for the presence of albuminuria.

KEY POINT

- Indications for kidney biopsy include glomerular hematuria, severely increased albuminuria, acute or chronic kidney disease of unclear cause, and kidney transplant dysfunction or monitoring.

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Item 9 Answer: A

Educational Objective: Treat severe preeclampsia.

The most appropriate treatment is to continue current therapy (**Option A**). Severe preeclampsia is identified by persistent systolic blood pressure (BP) >160 mm Hg or diastolic BP >110 mm Hg and end-organ damage. The HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome may represent a severe form of preeclampsia. In the HELLP syndrome, the hemolytic anemia, thrombocytopenia, and liver dysfunction are more prominent, whereas severe preeclampsia has greater BP elevations. This patient has severe preeclampsia with features of the HELLP syndrome. The appropriate initial therapy is rapid stabilization of severely elevated BP and intravenous magnesium followed by immediate delivery of the fetus. Magnesium sulfate is the drug of choice for seizure prophylaxis for women with acute-onset severe hypertension during pregnancy and the postpartum period. Starting magnesium should not be delayed in the setting of acute severe hypertension; it is recommended regardless of whether the patient has gestational hypertension with severe features, preeclampsia with severe features, or eclampsia. Acute kidney injury may persist for up to 48 hours following delivery; proteinuria may take months to resolve.

In large studies, intravenous dexamethasone therapy (**Option B**) has not been shown to be efficacious in treatment of severe preeclampsia or the HELLP syndrome.

Intravenous eculizumab (**Option C**) is indicated for patients with atypical hemolytic uremic syndrome with deficiencies in the complement cascade. Atypical hemolytic uremic syndrome does not cause liver dysfunction as seen in this patient.

Distinguishing the HELLP syndrome from thrombotic thrombocytopenic purpura (TTP) is important, as patients with TTP require fresh frozen plasma exchange (**Option D**) and glucocorticoids. TTP is very uncommon in pregnancy, typically presents earlier in gestation, and is marked by an even more profound decrease in hemoglobin and platelet count than seen in this patient.

Transfusion of packed red blood cells and platelets (**Option E**) is generally not recommended for patients in the absence of overt bleeding unless hemoglobin levels decrease to <7 g/dL (70 g/L) or platelet count decreases to <20,000/μL (20×10^9/L).

KEY POINTS

- Severe preeclampsia is identified by persistent systolic blood pressure >160 mm Hg or diastolic blood pressure >110 mm Hg and end-organ damage.
- Initial therapy for severe preeclampsia is magnesium, antihypertensive medication, and immediate delivery of the fetus.

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Item 10 Answer: A

Educational Objective: Treat gastroesophageal reflux disease in a patient with advanced chronic kidney disease.

The most appropriate additional therapy is famotidine (**Option A**). This patient has stage G4 chronic kidney disease (CKD) and symptoms of his gastroesophageal reflux disease (GERD). In patients with CKD, the nephrotoxic risk of medication or treatment used for comorbid medical conditions must be considered. As with all patients with GERD, first-line treatment should focus on lifestyle and diet modifications. Pharmacologic therapy includes antacids, H_2 blockers, and proton pump inhibitor (PPI) therapy. In this patient with significant symptoms, an H_2 blocker such as famotidine should be added to lifestyle modifications as treatment for GERD. In patients with advanced CKD, the dosing of H_2 blockers should be decreased or the dosing interval increased as guided by labeling instruction.

In addition to their classic association with acute interstitial nephritis/acute kidney injury, PPIs such as omeprazole (**Option B**) may contribute to the development and progression of CKD. The association has been observed in case-control studies and affirmed in a systematic review and meta-analysis. Although the evidence comes from observational studies, caution is still advised when considering PPI use in patients with advanced CKD, particularly when alternative therapies are available.

Over-the-counter oral antacids containing calcium carbonate and magnesium hydroxide (**Option C**) are commonly used to treat symptoms of GERD. However, patients with advanced CKD are at risk for magnesium toxicity with the use of these antacids and therefore should be avoided.

Sucralfate (**Option D**) is a sulfated polysaccharide complexed with aluminum hydroxide used in the treatment of peptic ulcer disease. Sucralfate binds to injured mucosal surface, promotes healing, and provides a barrier to peptic injury. Sucralfate is less effective than PPI therapy for peptic ulcer disease. Sucralfate has no role in the treatment of GERD due to its short duration of action and reduced effectiveness compared with other therapies, including PPIs and H_2 blockers. Finally, sucralfate contains aluminum, which may accumulate in patients with advanced CKD and is thus not recommended.

KEY POINTS

- Proton pump inhibitors may contribute to the development and progression of chronic kidney disease and should be avoided.
- H_2 blocker therapy can be considered for patients with advanced chronic kidney disease provided appropriate dosing is used.

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Item 11 Answer: B

Educational Objective: Treat a kidney stone with lithotripsy.

The most appropriate treatment is lithotripsy (**Option B**). A kidney stone >10 mm, as seen in this patient, is unlikely to pass into the bladder and must be removed promptly because there are signs of ureteral obstruction, which can result in kidney damage. Acute management of symptomatic nephrolithiasis is aimed at pain management and facilitation of stone passage. Pain can be relieved by NSAIDs and opioids as needed. Stone passage decreases with increasing size. Only 50% of stones >6 mm will pass, generally within 2 weeks, and stones >10 mm are extremely unlikely to pass spontaneously. Urologic intervention is required in all patients with evidence of infection, acute kidney injury, intractable pain, and stones that fail to pass. The most effective method for removal of this patient's stone is to break it up using either shock wave or laser lithotripsy. The former is noninvasive, whereas the latter is accomplished using an ureteroscope and requires anesthesia. Both methods have similar rates of stone clearance. Laser lithotripsy is more expensive but is associated with less postlithotripsy discomfort.

Administering intravenous 0.9% saline (**Option A**) would not be beneficial. There is no evidence that increasing urinary flow with the use of intravenous hydration results in a more rapid transit of kidney stones or decreased use of pain medication but may add to discomfort and patient inconvenience.

Although tamsulosin (**Option C**) has been used to facilitate stone passage, data suggest it may be less effective than previously believed reported. The data, however, remain controversial and, because risk is minimal, use of tamsulosin to aid in stone passage can still be considered. Trials of assisted passage may last up to 4 weeks. Regardless, this patient's stone is too large to pass into the ureter with or without tamsulosin therapy.

Observation (**Option D**) with frequent reevaluation may be an acceptable strategy for select patients with small stones and mild, easily managed pain, no evidence of infection, and no evidence of impending kidney damage. This patient has a stone that is too large to pass spontaneously and has evidence of hydroureter. Treatment with lithotripsy is a better option in this patient.

KEY POINTS

- Stone passage decreases with increasing size; only 50% of stones >6 mm will pass, and stones >10 mm are extremely unlikely to pass spontaneously.
- Urologic intervention is required in all patients with evidence of infection, acute kidney injury, intractable pain, stones that fail to pass, or large stones that are unlikely to pass.

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Item 12 Answer: C

Educational Objective: Diagnose drug-induced hypomagnesemia as a cause of hypokalemia.

This most likely cause of this patient's hypokalemia is secondary hypomagnesemia caused by pantoprazole (**Option C**). The potassium channel in the distal nephron is gated by magnesium and, in states of hypomagnesemia, remains open with subsequent renal losses of potassium. Hypomagnesemia has become increasingly recognized in patients taking proton pump inhibitors (PPIs) and is listed as a potential adverse effect in package inserts. The longer duration a person has been taking PPIs, the greater the likelihood of developing hypomagnesemia. Because urine magnesium levels are low in patients with hypomagnesemia, the presumed mechanism is believed to be inhibition of the magnesium transporters in the gastrointestinal tract. Recent genomic analysis has identified a genetic polymorphism in the TRMP 6 magnesium transporter in patients with PPI-induced hypomagnesemia. Until the hypomagnesemia is corrected, the kidney will continue to waste potassium, making correction of hypokalemia difficult.

Sodium-glucose transporter 2 (SGLT2) inhibitors such as canagliflozin (**Option A**) have been associated with a small increase in magnesium levels and would not be associated with this patient's hypomagnesemia. Patients with type 2 diabetes mellitus frequently have mild hypomagnesemia, which has been postulated to be secondary to insulin resistance. The cause of the increase in magnesium noted with SGLT2 inhibitors is unclear but may be related to improvement in insulin resistance or possibly a direct effect on magnesium transporters in the kidney.

Lisinopril (**Option B**), an ACE inhibitor, has minimal if any effect on magnesium levels. By decreasing aldosterone levels, these medications are associated with hyperkalemia.

Although diuretic use can cause both hypokalemia and hypomagnesemia, this is usually associated with a metabolic alkalosis. Because this patient's serum bicarbonate is not increased, surreptitious diuretic use (**Option D**) is a less likely cause of her hypokalemia.

KEY POINTS

- Proton pump inhibitors are a cause of hypomagnesemia, which typically occurs after long-term use.
- Magnesium deficiency is an important cause of hypokalemia.

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Item 13 Answer: D

Educational Objective: Manage chronic hypertension in a pregnant patient.

No further management other than clinical monitoring (**Option D**) is needed for this pregnant patient with chronic hypertension. Chronic hypertension is defined as hypertension starting before pregnancy or before 20 weeks of gestation. According to the American College of Cardiology/American Heart Association guidelines, and adopted by the American College of Obstetricians and Gynecologists (ACOG), the diagnosis of hypertension before pregnancy is based on systolic blood pressure >130 mm Hg and diastolic blood pressure >80 mm Hg. This patient is at 24 weeks' gestation and has no proteinuria or other evidence of end-organ damage; the diagnosis is most consistent with chronic hypertension. A 2014 Cochrane systematic review of 49 trials (4723 women) concluded that treatment of mild-to-moderate hypertension reduced the risk for developing severe hypertension but had no effect on the incidence of preeclampsia, preterm birth, fetal death, fetal growth restriction, or any other measured outcome. Antihypertensive treatment is not necessary at this time. For pregnant women with chronic hypertension, the 2019 ACOG Taskforce on Hypertension in Pregnancy recommends only treating persistent systolic blood pressure ≥160 mm Hg or diastolic ≥110 mm Hg to avoid overtreatment of hypertension and associated fetal risk. In the setting of comorbidities or underlying impaired kidney function, treating at lower blood pressure thresholds may be appropriate. Blood pressure goals with medications are 120-159/80-109 mm Hg. First-line agents are labetalol, nifedipine, and methyldopa.

Early delivery of the fetus (**Option A**) would be recommended if the patient had preeclampsia, which is defined by new-onset hypertension that occurs after 20 weeks' gestation associated proteinuria or end-organ damage. The absence of proteinuria and end-organ involvement in this patient is not consistent with preeclampsia.

Although thiazide diuretics such as hydrochlorothiazide (**Option B**) can be used in pregnancy, this patient's blood pressure does not warrant treatment at this time. Furthermore, diuretics are considered second-line antihypertensive agents during pregnancy and should be used with caution in pregnant patients, as they may induce oligohydramnios.

Labetalol (**Option C**) and other antihypertensive agents are not indicated, as treatment of chronic hypertension in pregnancy is not needed if the patient's blood pressure is <160/110 mm Hg and there is no evidence of end-organ damage, as seen in this patient.

KEY POINTS

- For pregnant women with chronic hypertension, guidelines recommend only treating persistent systolic ≥160 mm Hg or diastolic ≥110 mm Hg blood pressure in the absence of end-organ damage to avoid overtreatment of hypertension and associated fetal risk.
- Treatment of chronic hypertension (<160/110 mm Hg) during pregnancy is not associated with improved fetal outcomes.

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Item 14 Answer: C

Educational Objective: Diagnose white coat hypertension using ambulatory blood pressure monitoring.

The most appropriate management is to perform ambulatory blood pressure monitoring (ABPM) (**Option C**) to evaluate for white coat hypertension. White coat hypertension, also termed isolated clinic or office hypertension, refers to elevated blood pressure (BP) measured in the office, but normal out-of-office BP averages. According to guideline recommendations, in adults with untreated systolic BP >130 mm Hg but <160 mm Hg or diastolic BP >80 mm Hg but <100 mm Hg, it is reasonable to screen for white coat hypertension using either ABPM or home BP monitoring measurements obtained by the patient. Before white coat hypertension is diagnosed, the reliability of out-of-office measurements must be confirmed; for example, the patient's home BP monitor should be calibrated against the office sphygmomanometer or, preferably, BP should be measured by an ABPM device. In patients with white coat hypertension, annual follow-up with out-of-office BP measurements should be considered to determine if conversion to sustained hypertension has occurred.

Initiating chlorthalidone (**Option A**), a thiazide diuretic, is a reasonable initial therapy in patients with documented hypertension. Chlorthalidone is not indicated in this patient unless hypertension is confirmed using ABPM or home BP monitoring.

CT angiography, MR angiography, and duplex Doppler ultrasonography are imaging modalities used to diagnose renovascular hypertension. Routine testing for renovascular disease may not change management for patients with atherosclerotic renovascular disease, because data suggest that medical therapy may be as beneficial as invasive procedures. However, in young patients with resistant hypertension and a high clinical suspicion for fibromuscular dysplasia (e.g.,

sudden onset of resistant hypertension at a young age, presence of an abdominal bruit), renal artery imaging may be considered. This patient has no indication for renal artery imaging (**Option B**).

Rechecking this patient's BP in the office in 3 months (**Option D**) is not appropriate management, as elevated office BP should be confirmed using out-of-office measurements.

KEY POINTS

- White coat hypertension refers to elevated blood pressure measured in the office, but normal out-of-office measurements.
- In adults with untreated systolic blood pressure >130 mm Hg but <160 mm Hg or diastolic blood pressure >80 mm Hg but <100 mm Hg, it is reasonable to screen for white coat hypertension using either ambulatory blood pressure monitoring or home blood pressure monitoring.

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Item 15 Answer: A

Educational Objective: Treat hypermagnesemia in a patient with chronic kidney disease.

The most appropriate immediate treatment is intravenous calcium gluconate (**Option A**). Hypermagnesemia is defined by a serum magnesium level of >2.4 mg/dL (0.99 mmol/L). Hypermagnesemia occurs infrequently and most commonly results from excessive intake in the setting of decreased kidney function. Laboratory analysis often shows hypocalcemia. In patients with significant kidney disease, use of magnesium laxatives can cause significant elevation of serum magnesium levels and should be avoided in these patients. Many medications such as antacids and magnesium sulfate used in the treatment of refractory asthma and preeclampsia are other sources of magnesium. Hypermagnesemia decreases neural transmission, resulting in weakness, as seen in this patient, which can progress to paralysis. Hypermagnesemia also blocks calcium and potassium channels, resulting in hypotension and bradycardia. These effects become apparent when the serum magnesium level is >4.8 mg/dL (2.0 mmol/L). Prevention is the key to management of hypermagnesemia by avoiding magnesium-containing medications in patients with reduced kidney function. The immediate treatment for symptomatic hypermagnesemia is intravenous calcium gluconate. Calcium rapidly antagonizes the cardiovascular and neuromuscular effects of hypermagnesemia. This will allow time to set up and initiate hemodialysis, which is the definitive treatment to lower magnesium levels in patients with severe hypermagnesemia.

In patients with normal kidney function, intravenous furosemide (**Option B**), a loop diuretic, will increase kidney magnesium excretion; treatment would not be beneficial in this patient with late-stage chronic kidney disease.

Intravenous sodium bicarbonate (**Option C**) is associated with a decrease in ionized calcium. Although in vitro studies suggest a similar effect on ionized magnesium, human studies have not been done to support the use of sodium bicarbonate in the treatment of hypermagnesemia.

Patiromer (**Option D**) is a cation exchanger that is used to manage chronic elevations of serum potassium. Although patiromer has been associated with hypomagnesemia, this agent has a relative slow onset of action (1 to 4 hours) and would not be effective acutely and thus not an appropriate treatment for this patient.

KEY POINTS

- Hypermagnesemia decreases neural transmission, resulting in weakness, and blocks both calcium and potassium channels, resulting in hypotension and bradycardia.
- Symptomatic hypermagnesemia (serum magnesium level >4.8 mg/dL [2.0 mmol/L]) is immediately treated with intravenous calcium gluconate while awaiting hemodialysis.

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Item 16 Answer: A

Educational Objective: Treat acute kidney injury with renal replacement therapy.

The most appropriate renal replacement therapy (RRT) is continuous RRT (CRRT) (**Option A**). RRT is used to manage the urgent complications of severe acute kidney injury (AKI), including hyperkalemia, metabolic acidosis, volume overload refractory to diuretics, uremic manifestations, and dialyzable toxins. In patients with AKI, RRT options include intermittent hemodialysis (IHD); CRRT; "hybrid" therapies such as prolonged intermittent RRT (PIRRT); and peritoneal dialysis. This patient has AKI, metabolic acidosis, hyperkalemia, and volume overload. In patients who are hemodynamically unstable, CRRT is preferred because it is administered 24 hours per day, removing solutes and fluid much more slowly than IHD and resulting in better hemodynamic tolerance. However, randomized clinical trials have not shown a survival benefit of CRRT over IHD or PIRRT for critically ill patients with AKI.

Peritoneal dialysis (**Option B**) is not as effective as the other types of RRT but may be useful when other types are unavailable or vascular access cannot be obtained.

This patient has life-threatening electrolyte abnormalities and no immediate prospect of kidney function recovery. Therefore, continuation of current management (**Option C**) is unacceptable.

CONT.

All of the loop diuretics produce the same diuresis when given at equipotent doses. The patient has been unresponsive to escalating doses of furosemide; therefore, switching to another loop diuretic such as intravenous bumetanide (**Option D**) is unlikely to result in a significant diuresis and will not address this patient's acidemia.

KEY POINTS

- Continuous renal replacement therapy is a preferred modality of renal replacement therapy in patients with acute kidney injury and hemodynamic instability.
- Randomized clinical trials have not shown a survival benefit of continuous renal replacement therapy over intermittent hemodialysis or prolonged intermittent renal replacement therapy for critically ill patients with acute kidney injury.

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Item 17 Answer: C

Educational Objective: Identify laxative abuse as a cause of normal anion gap metabolic acidosis.

Laxative abuse (**Option C**) is the most likely cause of this patient's normal anion gap metabolic acidosis. Normal anion gap metabolic acidosis can be caused by gastrointestinal bicarbonate loss, renal loss of bicarbonate, or the inability of the kidney to excrete acid. The normal physiologic response to systemic acidosis is an increase in urine acid excretion. Therefore, an initial diagnostic step in normal anion gap metabolic acidosis is to determine whether the kidney is appropriately excreting acid. Increased acid excretion by the kidney is reflected as a marked increase in urine ammonium. However, urine ammonium measurement is difficult to obtain. Because ammonium carries a positive charge, chloride is excreted as the corresponding anion. Therefore, the amount of excreted chloride increases as urine ammonium levels increase. The urine anion gap can be used as an indicator of the ability of the kidney to excrete acid. The urine anion gap is calculated as follows:

$$\text{Urine Anion Gap} = (\text{Urine Sodium} + \text{Urine Potassium}) - \text{Urine Chloride}$$

In the context of increased urinary ammonium excretion, therefore, the urine anion gap will be negative. The negative urine anion gap in this patient (-6.0 mEq/L [-6.0 mmol/L]) suggests appropriate renal excretion of acid and therefore a gastrointestinal cause of the normal anion gap metabolic acidosis. In this patient, laxative abuse is a possible, even likely, explanation. In addition, the low urine potassium indicates appropriate renal compensation in context of laxative-induced hypokalemia.

Salicylate toxicity (**Option A**) would be associated with an anion gap, which is not present in this patient.

Surreptitious furosemide use (**Option B**) would be expected to result in a metabolic alkalosis, not metabolic acidosis.

Renal causes of normal anion gap metabolic acidosis are due to specific defects in bicarbonate reclamation (type 2 renal tubular acidosis [RTA]) or in hydrogen ion secretion (type 1 RTA). Topiramate (**Option D**) can cause both type 1 and type 2 RTA. The urine anion gap due to type 1 RTA is positive, which is not the case in this patient.

KEY POINTS

- Normal anion gap metabolic acidosis can be caused by gastrointestinal bicarbonate loss, renal loss of bicarbonate, or the inability of the kidney to excrete acid.
- A negative urine anion gap suggests appropriate kidney excretion of acid and therefore gastrointestinal bicarbonate loss as the cause of normal anion gap metabolic acidosis.

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Item 18 Answer: D

Educational Objective: Manage stable renovascular hypertension.

No additional diagnostic testing (**Option D**) is needed for this patient with stable renovascular hypertension. Clinical suspicion for renovascular hypertension is raised when patients >55 years of age present with onset of severe hypertension and develop acute kidney injury (AKI) after initiation of an ACE inhibitor or angiotensin receptor blocker (ARB), or after control of blood pressure (BP) to target goal. In addition, asymmetry >1.5 cm in kidney sizes on imaging or the presence of a kidney ≤9 cm can also increase the probability. Patients such as this one with evidence of atherosclerotic cardiovascular disease should receive medical therapy, including lifestyle interventions, low-dose aspirin, BP control, guideline-directed diabetes management, and high-intensity statin therapy. In patients with hypertension and chronic kidney disease (CKD) stage G3 or higher or stage G1 or G2 with albuminuria, treatment with an ACE inhibitor or ARB is recommended to slow kidney disease progression.

Three randomized trials (STAR, ASTRAL, and CORAL) failed to show that renal artery angioplasty (**Option A**) confers additional benefit above optimal medical therapy in patients with renovascular hypertension and stable kidney function. Patients who may benefit from percutaneous angioplasty or surgical intervention include those with a short duration of hypertension; atherosclerotic renovascular disease refractory to optimal medical therapy; severe hypertension or recurrent acute flash pulmonary edema; AKI following treatment with an ACE inhibitor or ARB; progressive impaired kidney function believed to be caused by

bilateral renovascular disease; or unilateral stenosis affecting a solitary functioning kidney. This patient has none of these indications. Finally, patients with advanced CKD or with proteinuria >1000 mg/g, such as this patient, are less likely to benefit from revascularization.

Although CT angiography and MR angiography (**Options B, C**) have higher diagnostic utility than ultrasonography, these imaging studies may be potentially harmful in patients with severe CKD, given the risk for contrast nephropathy and gadolinium-induced nephrogenic systemic fibrosis (with group 1 but not group 2 gadolinium-based contras media). Renal duplex Doppler ultrasonography is a reasonable imaging modality in these patients if performed by experienced sonographers. Additional testing for renal vascular disease is not required in this patient and is not cost-effective, given that no interventions other than continuing the current medical management will be undertaken.

KEY POINT

- In most patients with renal artery stenosis, the primary therapeutic intervention is medical management, including correction of modifiable cardiovascular risk factors.

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Item 19 Answer: E

Educational Objective: Manage acute interstitial nephritis in a patient taking multiple medications.

Naproxen and omeprazole should be discontinued (**Option E**). Acute interstitial nephritis (AIN) is a common cause of acute kidney injury (AKI) and is characterized by inflammation and edema of the interstitium. The classic clinical presentation of fever, rash, and peripheral eosinophilia occurs in only 10% to 30% of patients with AIN. Urinary findings can include eosinophiluria, leukocytes, erythrocytes, and leukocyte casts. Urine eosinophils are neither sensitive nor specific for AIN. Drug-induced AIN, especially due to antibiotics, is the most common cause of AIN. Other causes include infection, systemic disease, and autoimmune disorders. Typically, the serum creatinine level gradually increases 7 to 10 days after drug exposure. Drug-induced AIN from NSAIDs, including selective cyclooxygenase-2 inhibitors, is usually not associated with fever, rash, or eosinophilia and develops 6 to 18 months after drug exposure. AIN from NSAIDs can be associated with the nephrotic syndrome due to minimal change glomerulopathy or membranous nephropathy. Proton pump inhibitors are also associated with AIN without fever, rash, and eosinophilia. The onset of AIN with proton pump inhibitors is variable but typically occurs 10 to 11 weeks after exposure. Proton pump inhibitors are believed to be a risk factor for the development of chronic kidney disease.

Kidney recovery from drug-induced AIN is usually complete if the drug is discontinued immediately after the onset of kidney injury; however, recovery may take weeks to several months. Kidney biopsy should be considered if there is no improvement in kidney function after 5 to 7 days of drug discontinuation. Early glucocorticoid administration may limit damage associated with drug-induced AIN. When there are no obvious signs and symptoms of infection or toxic exposures, the most appropriate management is to discontinue high-probability medications and consider initiating a course of oral glucocorticoids. In patients taking multiple medications, it is reasonable to selectively discontinue the medications most likely causative of AIN. In this patient, the most appropriate course is to discontinue the naproxen and omeprazole.

Calcium channel blockers (amlodipine), statins (atorvastatin), and angiotensin receptor blockers (losartan) are rarely associated with AIN (**Options A-D**).

KEY POINTS

- Medications, especially antibiotics, are the most common cause of acute interstitial nephritis.
- Acute interstitial nephritis can be caused by NSAIDs and proton pump inhibitors in the absence of fever, rash, or eosinophilia.

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Item 20 Answer: E

Educational Objective: Diagnose proximal renal tubule dysfunction as a cause of hypophosphatemia.

The most likely cause of this patient's hypophosphatemia is proximal renal tubular dysfunction (**Option E**). This patient has ifosfamide-induced Fanconi syndrome. Ifosfamide metabolites are toxic to the proximal tubule, resulting in a generalized decrease in cell energetics and a decrease in transport of various substances across the luminal membrane, including phosphorus, glucose, amino acids, and protons. In addition to phosphate wasting, as identified by the fractional excretion of phosphorus >5%, this patient also has glycosuria despite having a normal serum glucose; this is commonly seen in patients with ifosfamide-induced Fanconi syndrome. The urinalysis finding of proteinuria is most likely secondary to the loss of amino acids in the urine. Mesna is a thiol compound that, when delivered intravenously, inactivates acrolein in the urine to reduce the risk for bladder toxicity from cyclophosphamide and ifosfamide. Although mesna can prevent the hemorrhagic cystitis, it has not been demonstrated to prevent the tubular toxicity. The treatment of the hypophosphatemia in this disorder requires large quantities of phosphorus, typically intravenously.

Chronic kidney disease (**Option A**) is associated with an increase in the serum phosphorus caused by a decrease

in filtered phosphorus; this patient has a decrease in serum phosphorus, which is inconsistent with chronic kidney disease as a cause for hypophosphatemia.

Three hormones are largely responsible for regulating calcium and phosphorus homeostasis: parathyroid hormone, vitamin D, and fibroblast growth factor 23 (FGF-23) (**Option B**). FGF-23 is a peptide secreted by various types of bone cells. It acts on the kidney to induce phosphaturia and downregulates 1α-hydroxylase to inhibit synthesis of 1,25-dihydroxyvitamin D. Although sarcomas have been associated with increased secretion of FGF-23 and severe phosphate wasting due to tumor-induced osteomalacia, this is extremely rare and would not explain the patient's glycosuria and proteinuria.

Intracellular shifts of phosphorus (**Option C**) can occur with administration of insulin, refeeding in individuals with starvation, or secondary to respiratory alkalosis; none of these factors is present in this patient.

Patients with diabetes mellitus and hyperglycemia may have hypophosphatemia caused by osmotic diuresis (**Option D**). However, this patient has no evidence of hyperglycemia or evidence of an ongoing osmotic diuresis such as hypotension or hypernatremia.

KEY POINT

- In patients with hypophosphatemia, proximal renal tubular phosphate dysfunction can be identified by a fractional excretion of phosphorus >5%.

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Item 21 Answer: B

Educational Objective: Diagnose glomerulonephritis.

The most appropriate test is kidney biopsy (**Option B**). This patient likely has glomerulonephritis. Glomerular hematuria typically features tea- or brown-colored urine with dysmorphic erythrocytes (or acanthocytes) and/or erythrocyte casts on urine sediment examination. Leukocyturia and leukocyte casts can be seen in patients, such as this one, with glomerulonephritis. Dysmorphic urinary erythrocytes are defined by their irregular (nonspherical) shape; acanthocytes are one type of dysmorphic erythrocyte. Erythrocyte casts are recognized by their cylindrical or tubular structure and inclusion of small, agranular spherocytes and, when present, are specific for hematuria of glomerular origin. Indications for kidney biopsy include glomerular hematuria, severely increased albuminuria, acute or chronic kidney disease of unclear cause (in the absence of atrophic kidneys), and kidney transplant dysfunction or monitoring. This patient with undiagnosed glomerular hematuria should have a kidney biopsy.

Cystoscopy (**Option A**) is indicated in the evaluation of gross or microscopic hematuria of nonglomerular origin. The presence of erythrocyte casts, proteinuria, and clinical features suggesting an underlying rheumatologic or autoimmune disease signifies glomerular bleeding and precludes the need for cystoscopy.

Ultrasonography (**Option C**) is the most commonly used kidney imaging modality. It is easily available, safe, and relatively inexpensive. Ultrasonography can demonstrate hydronephrosis, kidney size and cortical thickness, echogenicity, and presence of cysts and tumors. Absence of hydronephrosis quickly rules out obstruction in most cases. Echogenicity is the ability of a tissue to "bounce back" or return the ultrasound signal and is recognized as brighter shades on the sonogram image. Echogenicity is nonspecific but implies acute or chronic parenchymal disease. Ultrasonography is very useful in the evaluation of patients with undifferentiated acute kidney injury but is of limited usefulness in the evaluation of glomerulonephritis.

Leukocyte esterase is an enzyme present in leukocytes. A positive test suggests pyuria (≥5 leukocytes/hpf). A positive nitrite test signifies the presence of gram-negative bacteria capable of converting urine nitrates into nitrites. Dipstick analysis for urinary tract infection is most helpful when both the leukocyte esterase and nitrite tests are concordant. This patient's microscopic urinalysis reveals pyuria and accounts for the positive leukocyte esterase test. In this case, pyuria would be an expected finding in a patient with the nephritic syndrome. A urine culture (**Option D**) therefore is not needed.

KEY POINTS

- Glomerular hematuria typically features dysmorphic erythrocytes (or acanthocytes) and/or erythrocyte casts on urine sediment examination and is associated with proteinuria.
- Undiagnosed glomerular hematuria is an indication for a kidney biopsy.

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Item 22 Answer: A

Educational Objective: Treat hypertension in a Black patient who is unresponsive to initial therapy.

The most appropriate additional treatment is amlodipine (**Option A**). In this patient, a blood pressure (BP) target <130/80 mm Hg is reasonable. As initial therapy, thiazide diuretics or calcium channel blockers (CCBs) are preferred in Black patients without chronic kidney disease or heart failure. These drugs are more effective in lowering BP than are renin-angiotensin system (RAS) inhibitors (ACE inhibitors or angiotensin receptor blockers [ARBs]) or β-blockers and more effective in reducing cardiovascular events than are RAS inhibitors or α-blockers. Two or more antihypertensive medications are recommended to achieve a BP target of <130/80 mm Hg in most adults, especially Black adults, with hypertension. According to the American College of

Cardiology/American Heart Association guideline, four drug classes (thiazide diuretics, CCBs, ACE inhibitors, or ARBs) lower BP and reduce cardiovascular or renal outcomes. Except for the combination of ACE inhibitors and ARBs, regimens containing a combination of these classes are reasonable to achieve the BP target. Furthermore, the combination of an ACE inhibitor or ARB with a CCB or thiazide diuretic produces similar BP lowering in Black patients as in those of other racial or ethnic groups.

Doxazosin, hydralazine, and metoprolol (**Options B–D**) are not recommended drugs for either initial therapy or as add-on therapy in patients with hypertension, regardless of race or ethnicity, without the presence of compelling indications. Doxazosin might be considered in male patients with bothersome lower urinary symptoms due to benign prostatic hyperplasia; hydralazine and metoprolol in selected patients with heart failure; or metoprolol in patients with a recent myocardial infarction. None of these indications is present in this patient.

KEY POINTS

- In the absence of chronic kidney disease or heart failure, initial antihypertensive treatment with a thiazide diuretic or calcium channel blocker is recommended in Black patients.
- Except for the combination of ACE inhibitors and angiotensin receptor blockers (ARBs), regimens containing a combination of thiazide diuretics, calcium channel blockers, ACE inhibitors, and ARBs are preferred to achieve blood pressure goals in patients requiring dual antihypertensive therapy.

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Item 23 Answer: D

Educational Objective: Manage hyperphosphatemia in chronic kidney disease-mineral and bone disorder.

The most appropriate management is dietary restriction of phosphorus through a low phosphate diet (**Option D**). As kidney function declines, the normal homeostasis of calcium and phosphorus levels by the kidney becomes compromised, resulting in alterations in bone mineralization. The term chronic kidney disease-mineral and bone disorder (CKD-MBD) encompasses these changes. Parathyroid hormone (PTH) is the most important regulator of calcium and phosphorus concentrations. PTH stimulates osteoclasts to resorb bone, stimulates hydroxylation of 25-hydroxyvitamin D in the kidneys, and stimulates tubular reabsorption of calcium and induces renal phosphorus excretion. As CKD progresses, rising fibroblast growth factor 23 levels inhibit the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, resulting in lower intestinal absorption of calcium and phosphorus in the gut, contributing to hypocalcemia. Hypocalcemia is a potent stimulus for further increases in PTH levels. Increased PTH levels result in reduced calcium excretion, increased calcium absorption from the gut, increased phosphorus excretion by the kidneys, and activation of osteoclast bone resorption. As CKD progresses, the kidney is unable to compensate for the increased release of phosphorus from bone, and phosphorus levels rise. Disordered calcium and phosphate metabolism lead to several adverse pathologic effects, including vascular calcification, increased risk for cardiovascular events, and the altered-bone physiology of renal osteodystrophy. The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that, in patients with CKD stages G3a to G5, elevated phosphorus levels should be lowered toward the normal range. Treatment options include dietary modifications (phosphorus restriction) alone or in combination with the administration of phosphate binders.

KDIGO guidelines recommend against the use of activated vitamin D analogues such as calcitriol (**Option A**) in non-dialysis-dependent patients with CKD to avoid the risk of calcium overload; therefore, calcitriol should be avoided in this non-dialysis-dependent patient. These agents are routinely used in dialysis-dependent patients with end-stage kidney disease as CKD-MBD worsens.

For patients who remain hyperphosphatemic following dietary optimization, the next step is addition of a phosphate binder. The choice of a phosphate binder, calcium- or non-calcium-based, must be individualized for each patient. Calcium-based binders include calcium carbonate and calcium acetate (**Option B**); non-calcium-based binders include sevelamer (**Option E**) and lanthanum. However, data are lacking to guide clinicians in choosing calcium-based binders.

Cinacalcet (**Option C**), a calcimimetic that decreases PTH levels, is FDA approved for use in patients who are undergoing dialysis but not for use in patients with CKD.

KEY POINTS

- In patients with chronic kidney disease and hyperphosphatemia, the initial step in management is a low phosphate diet.
- In patients with chronic kidney disease who remain hyperphosphatemic following dietary optimization, the next step is addition of a phosphate binder.

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Item 24 Answer: C

Educational Objective: Diagnose chronic interstitial nephritis in agricultural communities.

Chronic interstitial nephritis (**Option C**) is the most likely diagnosis. Chronic interstitial nephritis in agricultural communities (CINAC; also known as Mesoamerican nephropathy)

is an emerging public health problem in many Central American and Asian countries. It is observed most commonly in young- to middle-aged male migratory agricultural workers and often progresses to end-stage kidney disease. This patient has many findings associated with chronic tubulointerstitial kidney disease. He is hypertensive and has a normal anion gap metabolic acidosis. Furthermore, his urinalysis demonstrates pyuria and low-grade proteinuria, and his kidney ultrasound shows nonspecific chronic kidney injury changes (increased cortical echogenicity and mild thinning). These findings, in the context of a patient who is a migratory agricultural worker in Central America, suggest that he has developed CINAC. Kidney biopsy may establish a definitive diagnosis.

Acute interstitial nephritis (**Option A**) is characterized by urine sediment containing leukocytes and leukocyte casts, unlike this patient's relatively bland urine sediment.

Although patients with acute bacterial infection may occasionally present with acute tubular necrosis (**Option B**), these patients typically have features of a systemic inflammatory response syndrome at the time of presentation and urine sediment showing granular casts.

IgA nephropathy (**Option D**) is a chronic glomerular disease typically characterized by microhematuria and occasional episodes of gross hematuria. This patient has a chronic tubulointerstitial disorder, not a glomerular disorder.

Infection-related glomerulonephritis (**Option E**), which may be seen concurrent with or following cellulitis, is accompanied by erythrocytes and erythrocyte casts in the urine sediment and often resolves after the acute infection resolves.

KEY POINTS

- Chronic interstitial nephritis in agricultural communities is most commonly observed in young- to middle-aged male agricultural workers and often progresses to end-stage kidney disease.
- Patients with chronic interstitial nephritis in agricultural communities may be hypertensive, and urinalysis may be normal or demonstrate pyuria and low-grade proteinuria.

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Item 25 Answer: B

Educational Objective: Treat hepatorenal syndrome.

The most appropriate additional treatment is intravenous albumin (**Option B**). This patient exhibits acute kidney injury (AKI) in the context of advanced cirrhosis. At this stage in her hospitalization, it is uncertain if she could have prerenal AKI, acute tubular necrosis, or hepatorenal syndrome (HRS). Type 1 HRS is a clinical diagnosis made after exclusion of other causes of kidney dysfunction. It is characterized by an increase in the serum creatinine level of at least 0.3 mg/dL (26.5 µmol/L) and/or ≥50% from baseline within 48 hours; bland urinalysis; and normal findings on kidney ultrasound. It is also supported by a lack of improvement in kidney function after withdrawal of diuretics and 2 days of volume expansion with intravenous albumin. Often, patients also have low urine sodium, low fractional excretion of sodium, and oliguria. Type 2 HRS is defined as a more gradual decline in kidney function associated with refractory ascites. General management includes discontinuing diuretics, restricting sodium, restricting water in hyponatremic patients, and searching for precipitating factors. Therapeutic interventions include treatment with vasoconstrictors and albumin.

Patients with HRS have an overall poor prognosis without liver transplantation. Hemodialysis (**Option A**) is typically not the best therapeutic option unless the patient is a liver transplant candidate.

Treatment of hepatorenal syndrome may also include the vasoconstrictors midodrine and octreotide (**Option C**) along with intravenous albumin to raise mean arterial pressure and improve kidney perfusion. However, midodrine and octreotide are not necessary in a patient such as this one who is receiving intravenous norepinephrine.

Although transjugular intrahepatic portosystemic shunt (**Option D**) is an effective therapy for some cases of refractory HRS, it is an invasive therapy with numerous potential complications that should not preempt the administration of albumin.

KEY POINTS

- Type 1 hepatorenal syndrome is characterized by an increase in the serum creatinine level of at least 0.3 mg/dL (26.5 µmol/L) and/or ≥50% from baseline within 48 hours; bland urinalysis; and normal findings on kidney ultrasound.
- Treatment of type 1 hepatorenal syndrome includes vasoconstrictors and intravenous albumin.

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Item 26 Answer: D

Educational Objective: Screen for skin cancer in a kidney transplant recipient.

The most appropriate screening test to perform next is a skin examination (**Option D**). This patient, who is at increased risk for multiple types of skin cancer, should be referred to a dermatologist or a clinician with special expertise for annual screening; screening frequency is increased for patients who have a history of skin cancer. Kidney transplant recipients are at increased risk for various complications due to their original underlying end-stage kidney disease and the use of chronic immunosuppressive medications, which may be

related to risks for altered immune surveillance or idiosyncratic medication side effects. Kidney transplant recipients are at increased risk for several other malignancies, including renal cell carcinoma, colon cancer, lung cancer, thyroid cancer, anogenital cancers, and posttransplant lymphoproliferative disease. These patients are also at increased risk for cardiovascular disease, and those treated with glucocorticoids, calcineurin inhibitors, and mTOR inhibitors are at increased risk for new-onset diabetes after transplant (NODAT).

The U.S. Preventive Services Task Force (USPSTF) recommends screening for colorectal cancer in asymptomatic adults aged 50 to 75 years. The USPSTF supports using the test that is most likely to result in completion of screening. Options include colonoscopy (**Option A**), flexible sigmoidoscopy, CT colonography, stool-based testing, and combination of stool-based testing and flexible sigmoidoscopy. This patient should be screened for colon cancer beginning at 50 years of age.

A low-dose chest CT (**Option B**) to screen for lung cancer is not indicated. Although patients on immunosuppressive medications are at increased risk for various cancers, screening for non-skin cancers should follow guidelines for the general population. The criteria for screening include those who are aged 55 to 74-80 years (guidelines differ on ages to discontinue screening), have at least a 30-pack-year smoking history, and are current smokers or have quit within the last 15 years.

Kidney transplant recipients are at risk for NODAT. Posttransplant fasting glucose and symptoms should be monitored. Fasting glucose is monitored more frequently in the first year after transplant and then annually in the absence of symptoms to suggest hyperglycemia. The diagnosis of NODAT is made based on the same criteria as that for the general population. An oral glucose tolerance test (**Option C**) is not indicated for this patient with a normal fasting blood glucose.

KEY POINTS

- Kidney transplant recipients are at increased risk for multiple types of skin cancer and should undergo annual skin examination.
- Although patients on immunosuppressive medications are at increased risk for various cancers, screening for non-skin cancers should follow guidelines for the general population.

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Item 27 Answer: A

Educational Objective: Treat IgA nephropathy with blockade of the renin-angiotensin system.

First-line therapy for IgA nephropathy (IgAN) is initiation of antiproteinuric therapy with blockade of the renin-angiotensin system using either an ACE inhibitor, such as lisinopril (**Option A**), or an angiotensin receptor blocker (ARB) and is the most appropriate management for this patient. In patients with proteinuria, treatment with ACE inhibitors or ARBs lowers intraglomerular pressure resulting in decreased protein excretion and often slows the rate of declining kidney function. Acute decline in glomerular filtration rate and hyperkalemia are well-recognized potential adverse effects of these drugs, mandating monitoring of serum creatinine and potassium levels. Antiproteinuric therapy is usually coupled with lipid-lowering therapy and fish oil, although the efficacy of the latter two as specific IgAN therapies is unproven.

Mycophenolate mofetil (**Option B**) is reserved as a second- or third-line therapy for patients with IgAN who decline despite glucocorticoid or other immunosuppression. This treatment has only shown benefit in patients of Asian descent.

Despite its purported anti-inflammatory properties, the benefit of treating IgAN with omega-3 fatty acids (fish oil) (**Option C**) is unclear. Because of its safety, it can be used in conjunction with other therapies but should not be the exclusive treatment of IgAN.

Immunosuppressive therapy, such as prednisone (**Option D**), would not be used for this patient. Although two thirds of patients with IgAN will have progressive loss of kidney function, the use of immunosuppressive therapy remains controversial. Small studies have shown that a 6-month course of prednisone reduces proteinuria and slows decline in glomerular filtration rate in patients with IgAN and >1000 mg/24 h proteinuria despite maximal therapy with an ACE inhibitor or ARB. However, two large randomized controlled trials (STOP-IgAN and TESTING) called into question this management. The STOP-IgAN study showed no difference in changes in kidney function between those patients with IgAN treated with or without immunosuppression over a 3-year period. The TESTING study was terminated early due to significantly higher rates of adverse events in patients with IgAN who were treated with prednisone. As a result, treatment efficacy could not be determined. Because this patient has not yet been treated with an ACE inhibitor or ARB, consideration of immunosuppressive therapy with prednisone is premature.

KEY POINTS

- First-line therapy for IgA nephropathy is either an ACE inhibitor or an angiotensin receptor blocker.
- Treatment of IgA nephropathy with high-dose glucocorticoids is associated with an increased risk for adverse events and may not improve kidney function.

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Item 28 Answer: C

Educational Objective: Treat acute hyponatremia.

The most appropriate management is a 100-mL bolus of 3% saline (**Option C**). Symptoms caused by hyponatremia

depend on both the rapidity and degree of decline in serum sodium. A sudden drop in serum sodium causes water to move into the brain, producing cerebral edema and possibly causing headaches, seizures, or death. Hyponatremia has been reported in inexperienced marathon runners who overhydrate. A systematic study of hyponatremia in runners finishing a marathon revealed that 13% had a serum sodium concentration of ≤135 mEq/L (135 mmol/L) and 0.6% had critical hyponatremia of ≤120 mEq/L (120 mmol/L). Hyponatremia was associated with consumption of more than 3 liters of fluids during the race, consumption of fluids every mile, and a racing time of more than 4 hours, which is a possible indication of less training. Female runners remain a readily identifiable risk group in many studies, but this may represent the impact of body size and longer racing time rather than the sex of the athlete. The other major factor causing hyponatremia in endurance athletes is persistent secretion of antidiuretic hormone (ADH). Because hyponatremia is not uncommon with extreme exercise and overhydration, it is important that medical personnel are able to measure sodium rapidly. If the patient's sodium cannot be measured, treatment should be held until the patient can be transported to a facility where sodium measurements can be made. Individuals with severe symptoms (e.g., confusion, coma, seizures) secondary to acute hyponatremia should be treated with a 100-mL bolus of 3% saline. If symptoms do not improve and the sodium remains low, an additional bolus can be given.

Although fluid restriction (**Option A**) may allow for correction of serum sodium in persons with minimal symptoms, it should never be the sole treatment when severe symptoms such as confusion are present, as they are in this patient.

Intravenous 0.9% saline (**Option B**) should not be administered in this patient. If her ADH levels are extremely elevated, her urine osmolality will exceed the osmolality of normal saline. Intravenous 0.9% saline could potentially lower the patient's sodium further. The use of 0.9% saline should be limited to those patients with evidence of volume depletion and minimal symptoms.

It is inappropriate to not treat this patient (**Option D**). This patient's serum sodium is 130 mEq/L (130 mmol/L), and serious neurologic symptoms may occur when the sodium decreases acutely to <132 mEq/L (132 mmol/L). Therefore, this patient needs prompt treatment.

KEY POINTS

- Acute hyponatremia developing in less than 48 hours can cause headaches, seizures, or death.
- Acute hyponatremia should be treated with a 100-mL bolus of 3% saline.

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Item 29 Answer: D

Educational Objective: Evaluate chronic kidney disease.

The most appropriate test to help diagnose the cause and assess the prognosis of this patient's chronic kidney disease (CKD) is a spot urine albumin-creatinine ratio (**Option D**). CKD is defined as abnormal kidney structure or function present for >3 months. CKD is stratified into stages 1 to 5 based on the level of estimated glomerular filtration rate (eGFR). Because albuminuria is associated with increased renal and cardiovascular morbidity and mortality, eGFR-based kidney stages are modified by the degree of albuminuria. This dual eGFR and albuminuria-staging matrix provides a means for predicting which patients are at highest risk for developing end-stage kidney disease. This patient has CKD confirmed by a persistently low eGFR for at least 6 months. A spot urine albumin-creatinine ratio should be obtained to determine the degree of proteinuria. In addition to prognostication, this test will help categorize his CKD as nephrotic or non-nephrotic, which will inform diagnostic testing.

Controlling hyperglycemia in patients with diabetes mellitus will slow the progression of CKD. Although a hemoglobin A_{1c} measurement (**Option A**) is important in the management of diabetes, it is not the most appropriate test to determine the cause and prognosis of CKD.

Kidney biopsy (**Option B**) is used to determine the cause of CKD when a glomerulonephritis or unexplained tubulointerstitial disease is likely. Kidney biopsy is not indicated in the presence of shrunken kidneys (<9 cm), which generally indicate chronic irreversible disease. Consideration of a kidney biopsy is premature for this patient, pending results of kidney ultrasonography, urine albumin-creatinine ratio, and ophthalmology examination. If retinopathy is confirmed by a dilated retinal examination and the patient has albuminuria, the most likely diagnosis in this patient with long-standing diabetes is diabetic kidney disease.

Serum parathyroid hormone (**Option C**), calcium, phosphorus, and 25-hydroxyvitamin D levels are indicated for management of CKD-mineral and bone disorder. Although these laboratory studies are indicated for all patients with CKD, they are not used as tests to help determine the prognosis of CKD.

KEY POINTS

- Chronic kidney disease is defined as abnormal kidney structure or function present for >3 months.
- In patients with chronic kidney disease, albuminuria is associated with increased renal and cardiovascular morbidity and mortality.

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Item 30 Answer: A

Educational Objective: Treat a hypertensive emergency with aortic dissection.

The most appropriate initial treatment is to administer intravenous (IV) esmolol (**Option A**). This patient has a hypertensive emergency with a type A aortic dissection involving the ascending aorta. For hypertensive emergency with evidence of end-organ damage, blood pressure (BP) should be rapidly lowered using IV short-acting agents. Esmolol is a β_1-selective adrenergic receptor blocker with a 1- to 2-minute onset of action. Esmolol can rapidly reduce heart rate and BP, thereby reducing aortic wall sheer stress and limiting the propagation of the dissection. The 2017 American College of Cardiology/American Heart Association BP guideline recommends that for adults with a compelling condition (such as aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis), systolic BP should be reduced to <140 mm Hg during the first hour and to <120 mm Hg in aortic dissection. Referral for emergency surgery should be considered in all patients with type A aortic dissection given the very high mortality rate associated with this condition.

Hydralazine (**Option B**) can increase myocardial contractility and is not the first-line treatment in this case.

Treatment with an IV rapidly acting calcium channel blocker such as nicardipine (**Option C**) or with a vasodilator such as nitroprusside (**Option D**) should not be initiated before β-blockade. In the absence of β-blockade, vasodilator therapy induces reflex activation of the sympathetic nervous system, resulting in tachycardia and enhanced ventricular contraction, which increases aortic wall shear stress. Following effective β-blockade, vasodilator therapy can be initiated to reduce the systolic BP to <120 mm Hg.

KEY POINTS

- Intravenous short-acting β_1-selective adrenergic receptor blockers are an initial first-line treatment to rapidly lower blood pressure in patients with hypertensive emergency and aortic dissection.
- In adults with a compelling condition (such as aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis), systolic blood pressure should be reduced to <140 mm Hg during the first hour and to <120 mm Hg in aortic dissection.

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Item 31 Answer: D

Educational Objective: Diagnose type 2 (proximal) renal tubular acidosis.

The most likely cause of this patient's laboratory findings is type 2 (proximal) renal tubular acidosis (RTA) (**Option D**). Type 2 RTA involves a proximal tubular defect in reclaiming bicarbonate and is characterized by a normal anion gap metabolic acidosis, hypokalemia, glycosuria (without hyperglycemia), low-molecular-weight proteinuria, and renal phosphate wasting (known as Fanconi syndrome when all features are present). Because distal urine acidification remains intact, the urine pH is usually <5.5 without alkali therapy, and the urine anion gap ([Urine Sodium + Urine Potassium] – Urine Chloride) would be negative, reflecting increased excretion of acid in the form of ammonium and chloride. This patient's normal anion gap metabolic acidosis, low urine pH, hypokalemia, and hypophosphatemia makes type 2 RTA most likely. Type 2 RTA in this case is likely due to multiple myeloma–associated light chain proximal tubulopathy. Multiple myeloma is suggested by the presence of anemia and high gamma globulin fraction (elevated total protein and low albumin concentrations).

Bartter syndrome (**Option A**) can cause hypokalemia and hypophosphatemia but is also associated with metabolic alkalosis and most often presents in childhood. Liddle syndrome (**Option B**) causes increased sodium reabsorption in the distal nephron with resulting hypertension, metabolic alkalosis, and potassium wasting. This patient has a normal anion gap metabolic acidosis, which excludes Bartter and Liddle syndromes.

Type 1 (hypokalemic distal) RTA (**Option C**) is due to a defect in urine acidification in the distal nephron. Because of the inability to excrete hydrogen ions, patients develop a metabolic acidosis with compensatory hyperchloremia, resulting in a normal anion gap and the inability to acidify urine below a pH of 6.0; this patient's urine pH is 5.0. The urine anion gap is positive, reflecting decreased acid excretion in the form of ammonium and chloride. The same defects also cause potassium wasting, and the increased proximal resorption of citrate that occurs with metabolic acidosis leads to hypocitraturia and increased risk for calcium phosphate kidney stones and nephrocalcinosis.

Type 4 (hyperkalemic distal) RTA (**Option E**) due to aldosterone deficiency or resistance is associated with a mild normal anion gap metabolic acidosis and hyperkalemia, which are not seen in this patient.

KEY POINTS

- Type 2 (proximal) renal tubular acidosis is characterized by a normal anion gap metabolic acidosis, hypokalemia, glycosuria (without hyperglycemia), low-molecular-weight proteinuria, and renal phosphate wasting.
- Type 1 (hypokalemic distal) renal tubular acidosis is characterized by a normal anion gap metabolic acidosis, hypokalemia, urine pH >6.0, and calcium phosphate kidney stones.

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Item 32 Answer: B

Educational Objective: Treat stage 2 hypertension with combination drug therapy.

The most appropriate additional therapy is amlodipine-valsartan (**Option B**). This patient has stage 2 hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg). For patients with stage 2 hypertension with or without cardiovascular risk or disease, pharmacologic management in addition to therapeutic lifestyle interventions is recommended. The 2017 American College of Cardiology/American Heart Association blood pressure (BP) guideline recommends combination therapy with two first-line antihypertensive drugs of different classes for adults with stage 2 hypertension and an average BP that is 20/10 mm Hg above their BP target. Based on the presence of hypertension, dyslipidemia, and cigarette smoking, this patient has a calculated 10-year atherosclerotic cardiovascular disease (ASCVD) event risk of 10%. The target BP for patients with established cardiovascular disease or for patients with an estimated ASCVD event risk ≥10% is 130/80 mm Hg. This patient has an elevated 10-year ASCVD event risk and his BP is >20/10 mm Hg above target; therefore, combination drug therapy is indicated. To maximize adherence, using a fixed-dose combination agent may be more effective than adding two separate antihypertensive agents.

Starting chlorthalidone, amlodipine, or valsartan (**Options A, C, D**) as single-agent therapy would each be appropriate as first-line therapy for patients with stage 1 hypertension (systolic BP of 130-139 mm Hg or diastolic BP of 80-89 mm Hg). Combination therapy is recommended for patients with stage 2 hypertension and an average BP that is 20/10 mm Hg above their BP target.

KEY POINTS

- A blood pressure <130/80 mm Hg is recommended for adults with hypertension and cardiovascular disease or a 10-year atherosclerotic cardiovascular disease event risk ≥10%.
- Combination therapy with two first-line antihypertensive medications of different classes is recommended for adults with stage 2 hypertension and an average blood pressure (BP) of >20/10 mm Hg above BP target.

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Item 33 Answer: A

Educational Objective: Evaluate gross hematuria.

Cystoscopy (**Option A**) is the most appropriate diagnostic test to perform next in this patient. Hematuria is frequently encountered among adults in ambulatory care. Macroscopic hematuria should prompt urology referral even if self-limited. Hematuria is most often of nonglomerular origin. If a nephrologic cause of hematuria is not suggested, it may indicate a malignancy. Guidelines from the American Urological Association recommend that patients ≥40 years of age or of any age with risk factors for lower urinary tract malignancy (such as irritative voiding symptoms, smoking history, aniline dye exposure, or cyclophosphamide exposure) undergo evaluation for malignancy with imaging. If imaging is negative, cystoscopy should be performed. This patient is a 43-year-old man without evidence of glomerular disease (no proteinuria or increased serum creatinine level) or infection (no leukocyturia, negative nitrites, and no leukocyte esterase) and negative imaging of the upper genitourinary tract. Therefore, it is appropriate to assess for bladder pathology using cystoscopy.

Kidney biopsy (**Option B**) in a patient with hematuria is not indicated in the absence of evidence of glomerular disease. A glomerular origin is suggested by concurrent proteinuria, presence of dysmorphic erythrocytes, increased serum creatinine, or decrease in estimated glomerular filtration rate. This patient has no indication for a kidney biopsy.

Repeat urinalysis (**Option C**) is not indicated. This patient's macroscopic hematuria should prompt urologic investigation now. A single incident of hematuria warrants further investigation, even if the patient has a bleeding disorder or is receiving antiplatelet or anticoagulation therapy. If menstruation, viral illness, urinary tract infection, vigorous exercise, or another benign cause is suspected, urinalysis should be repeated after the cause is resolved. Otherwise, as in this case, further evaluation should ensue without additional urinalysis.

The absence of proteinuria makes a glomerular cause of hematuria less likely. Although a 24-hour urine protein collection (**Option D**) is the gold standard for determining proteinuria, random urine albumin-creatinine ratio and protein-creatinine ratio correlate well with timed collections. This patient has a normal urine protein-creatinine ratio; therefore, a 24-hour collection is not indicated.

KEY POINTS

- Patients with gross hematuria who are >35 years of age or have risk factors for lower urinary tract malignancy should be evaluated for malignancy.
- Evaluation of gross hematuria includes imaging of the lower urinary tract followed by cystoscopy if imaging is negative.

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Item 34 Answer: D

Educational Objective: Manage hepatitis C virus infection in a patient with end-stage kidney disease.

The most appropriate management is to discuss hepatitis C virus (HCV) treatment and timing (**Option D**). This patient

has evidence of HCV infection and hepatitis B virus (HBV) immunity (negative hepatitis B surface antigen, positive hepatitis B surface antibody). Screening patients for both viruses on admission to a dialysis center is part of ongoing infection control surveillance within a dialysis center. Identification of infection is important because treatment can be offered. All patients with HCV infection should be considered for treatment unless there are significant life-limiting comorbidities. Treatment regimens for HCV infection include a combination of direct-acting antivirals, using different mechanisms to prevent viral reproduction. Regimens are chosen based on genotype, previous treatment experience and response, and fibrosis status. The timing of HCV treatment must be individualized in patients such as this one with end-stage kidney disease (ESKD) who are potential kidney transplant recipients. It is important to discuss treatment and treatment timing with this patient and the kidney transplant program. In patients with ESKD, treatment for concurrent HCV infection can be timed before kidney transplantation or after transplantation if receiving an HCV-infected donor kidney.

Antiviral treatment is safe and generally well tolerated in patients with ESKD, and the presence of HCV infection is not a contraindication for kidney transplantation. Neither avoiding antiviral therapy nor transplantation is appropriate for this patient (**Option A**).

First-line treatment for HBV infection is entecavir (**Option B**) or tenofovir. However, this patient is immune to hepatitis B, and treatment is not warranted.

Pegylated interferon and ribavirin (**Option C**) would not be indicated for this patient before a discussion about the timing of HCV therapy. In addition, many direct-acting antiviral regimens are available and are safe for use in patients with chronic kidney disease or ESKD with significantly less morbidity compared with interferon therapy.

KEY POINT

- In patients with end-stage kidney disease, treatment for concurrent hepatitis C virus infection can be timed before kidney transplantation or after transplantation if receiving a hepatitis C–infected donor kidney.

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Item 35 Answer: A

Educational Objective: Diagnose postrenal obstructive uropathy.

The most appropriate initial step in management is bladder ultrasonography (**Option A**). This patient most likely has postrenal obstructive uropathy secondary to benign prostatic hyperplasia (BPH) and the recent introduction of chlorpheniramine, a drug with anticholinergic properties. Postrenal acute kidney injury (AKI) results from urinary tract obstruction. If left uncorrected, the elevated tubular pressure can cause chronic and end-stage kidney disease. Postrenal obstruction due to bladder outlet obstruction should be suspected in patients with a history of BPH and diabetes mellitus (neurogenic bladder). Symptoms of bladder outlet obstruction may include abdominal fullness or pain; urinary frequency, urgency, and hesitancy; nocturia; and incomplete voiding. The diagnosis is supported by a distended bladder and prostate enlargement on physical examination. In postrenal obstruction, urine sediment is often unremarkable, but microscopic hematuria may be present. Bladder outlet obstruction is confirmed by an elevated postvoid residual bladder volume by ultrasonography. If the obstruction is relieved within 1 to 2 weeks, recovery of kidney function is excellent.

Obstruction of the upper tract (ureters or renal pelvis) must be bilateral to cause AKI (unless obstruction occurs in a single kidney); causes may include nephrolithiasis, abdominal or pelvic surgeries or radiation, pelvic malignancies, or retroperitoneal fibrosis or lymphadenopathy. Kidney ultrasonography (**Option B**) is the initial modality of choice for diagnosing upper tract obstruction. Although kidney ultrasonography may ultimately be performed, the next management step is bladder ultrasonography and possible bladder catheterization because bladder outlet obstruction is more likely to occur in a man with BPH recently exposed to a medication with anticholinergic effects.

IgG4-related autoimmune pancreatitis can be associated with other IgG4-related diseases, including retroperitoneal fibrosis and obstructive uropathy. CT with contrast or MRI of the abdomen and pelvis (**Option C**) are the initial imaging studies. However, in this patient with BPH, the initial diagnostic modality is bladder ultrasonography. Failure to establish a diagnosis should prompt appropriate imaging tests.

Patients with acute ureteral obstruction caused by nephrolithiasis may present with ureteral colic. In this scenario, a noncontrast CT of the abdomen and pelvis (**Option D**) may provide the correct diagnosis. However, there are no symptoms to support this diagnosis, and bladder ultrasonography will establish the most likely diagnosis.

KEY POINTS

- Postrenal acute kidney injury results from urinary tract obstruction that is readily reversible if recognized early and corrected promptly.
- Postrenal obstruction should be suspected in patients with a history of benign prostatic hyperplasia, diabetes mellitus, nephrolithiasis, abdominal or pelvic surgeries or radiation, pelvic malignancies, or retroperitoneal fibrosis or lymphadenopathy.

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Item 36 Answer: A

Educational Objective: Diagnose focal segmental glomerulosclerosis.

The most likely diagnosis is focal segmental glomerulosclerosis (FSGS) (**Option A**). In the United States, FSGS currently accounts for up to 40% of primary nephrotic syndromes in adults. FSGS is the most common form of the nephrotic syndrome in Black patients. Individuals of African ancestry carry approximately a five times higher risk for FSGS than those of European descent, likely mediated in large part by variants in the *APOL1* gene, which is likely responsible for this patient's FSGS as well as the kidney disease found in other members of his family. Black persons develop kidney failure at rates four to five times higher than White persons, and the *APOL1* gene is attributed to a large fraction of this health disparity. Two risk alleles for kidney disease (G1 and G2) have been identified in the *APOL1* gene. The transmission of disease risk is consistent with recessive inheritance. Approximately 12% to 15% of African Americans inherit a high-risk *APOL1* genotype; this accounts for a large fraction of nondiabetic kidney disease in African Americans that in the past has been attributed to hypertension but would appear as FSGS on biopsy. Persons with a high-risk *APOL1* genotype have an approximately 10-fold increased risk for FSGS and a 7-fold increased risk for hypertension-attributed end-stage kidney disease.

Kidney involvement in systemic lupus erythematosus (SLE) is common, and lupus nephritis (LN) (**Option B**) is a major source of morbidity. Patients typically present with extrarenal symptoms of SLE at the time of diagnosis of LN, with active lupus serologies and low complement levels. Occasionally, LN may be the initial manifestation. Patients with class I or II LN may have minimal or no kidney findings, and those with class III or IV present with varying degrees of the nephritic syndrome. Patients with class V LN typically present with proteinuria.

Membranous nephropathy (MN) (**Option C**) is the most common cause of idiopathic nephrotic syndrome in adult White persons. MN may also be associated with infections (hepatitis B and C, malaria, syphilis), SLE, medications (gold salts, NSAIDs), and malignancies (solid tumors, lymphomas). In most patients with idiopathic MN, circulating antibodies directed to podocyte surface antigens (phospholipase A2 receptor) activate complement and damage the glomerular basement membrane.

Minimal change glomerulopathy (MCG) (**Option D**) is the most common cause of idiopathic nephrotic syndrome in children and accounts for approximately 10% of cases in adults. Secondary causes of MCG include medications (NSAIDs, lithium, pamidronate, the interferons) and malignancies (Hodgkin lymphoma and thymoma).

KEY POINT

- Focal segmental glomerulosclerosis is the most common form of the nephrotic syndrome in Black patients, likely mediated in large part by variants in the *APOL1* gene.

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Item 37 Answer: D

Educational Objective: Treat hypertension in a patient with diabetes mellitus and albuminuria using an ACE inhibitor or angiotensin receptor blocker.

The most appropriate treatment is to begin losartan (**Option D**). Blood pressure (BP) control is more difficult to achieve in patients with diabetes mellitus, necessitating use of combination therapy in most of these patients. The 2017 American College of Cardiology/American Heart Association guideline recommends a target BP of <130/80 mm Hg for patients with hypertension and diabetes. The American Diabetes Association (ADA) recommends that most patients with diabetes and hypertension should be treated to a target BP of 140/90 mm Hg; 130/80 mm Hg may be appropriate for individuals at higher risk (existing atherosclerotic cardiovascular disease [ASCVD] or 10-year ASCVD risk ≥15%), if it can be achieved safely. In adults with diabetes and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, angiotensin receptor blockers [ARBs], and calcium channel blockers) are useful and effective. ACE inhibitors or ARBs are the preferred drug classes for treatment of hypertension for patients with diabetes and albuminuria (albumin-creatinine ratio ≥300 mg/g) and in adults with hypertension and chronic kidney disease (stage G3 or higher or stage G1 or G2 with albuminuria) to slow kidney disease progression. Among the drug classes, ACE inhibitors and ARBs have the best efficacy on urinary albumin excretion and demonstrate a significant reduction in disease progression. The ADA also recommends use of an ACE inhibitor or ARB at the maximum tolerated dose indicated as first-line treatment for hypertension in patients with diabetes and albuminuria.

Although first-line therapy in patients with diabetes can include a thiazide diuretic or a calcium channel blocker (e.g., amlodipine) (**Option A**), the presence of albuminuria is an indication for the addition of a renin-angiotensin system inhibitor such as losartan.

Due to the absence of outcome data, β-blockers such as atenolol (**Option B**) are not usually recommended as initial antihypertensive medication therapy. However, they can be used in special populations, such as patients with a previous myocardial infarction or heart failure, in which outcome data exist.

Doxazosin (**Option C**) is not a typical second drug added to thiazide diuretic therapy because of its side-effect profile, which includes orthostatic hypotension. In addition, doxazosin is not as efficacious as ACE inhibitors or ARBs in preventing the progression of kidney disease.

KEY POINTS

- In adults with diabetes mellitus and hypertension, diuretics, ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers are all effective agents.
- ACE inhibitors or angiotensin receptor blockers are the preferred drug classes for treatment of hypertension in patients with diabetes mellitus and albuminuria.

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Item 38 Answer: B

Educational Objective: Diagnose urinary tract infection caused by a urea-splitting organism.

Proteus mirabilis (**Option B**) is the most likely organism responsible for this patient's infection. This patient most likely has a urinary tract infection (UTI) caused by *Proteus*, or other urea-splitting organisms such as *Klebsiella* or, less frequently, *Pseudomonas*. These bacteria secrete urease, which enzymatically hydrolyzes urea into carbon dioxide and ammonium, which markedly increases urine pH and results in the precipitation of magnesium ammonium phosphate, also known as struvite. On urinalysis, the urine pH will be >7.5. Struvite crystals are recognized by their coffin-lid appearance. Struvite crystals can rapidly form large stones in the renal pelvis and are responsible for the creation of staghorn calculi, which are stones that bridge two or more renal calyces. Because struvite stones are large and grow rapidly, they do not pass into the ureter to cause pain typical of smaller stones. Struvite stones form most commonly in women, and women are more likely than men to develop upper UTI. Other predisposing conditions include urinary stasis from a neurogenic bladder, as seen in this patient. Patients with infection caused by urea-splitting organisms have the typical signs and symptoms of UTI. However, these stones may become persistently infected despite antibiotic therapy and are a source of significant morbidity and mortality due to sepsis. Percutaneous nephrolithotomy is the first-line treatment for most patients.

In 95% of cases, UTIs are caused by a single bacterial species, mainly gram-negative aerobic bacilli originating from the bowel. Uropathogenic *Escherichia coli* (**Option A**) accounts for 75% to 95% of UTIs in women. Less common urinary pathogens include other members of the Enterobacteriaceae family, staphylococci (most often *Staphylococcus saprophyticus*) (**Option C**), streptococci (in particular *Streptococcus agalactiae*) (**Option D**), and enterococci. UTIs occurring in hospitals and long-term care facilities frequently involve a more varied group of organisms (such as *Enterobacter, Providencia, Morganella, Citrobacter, Serratia*, and *Pseudomonas*). These bacteria are not associated with crystal formation.

KEY POINTS

- Infection with urea-splitting organisms such as *Proteus, Klebsiella*, and *Pseudomonas* increases urine pH and results in the precipitation of magnesium ammonium phosphate, also known as struvite.
- Struvite crystals in the urine are recognized by their characteristic coffin-lid appearance.

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Item 39 Answer: D

Educational Objective: Treat hypertension in a patient with type 2 diabetes mellitus and albuminuria.

The most appropriate initial therapy is lisinopril (**Option D**), an ACE inhibitor, to treat hypertension in this patient with type 2 diabetes mellitus and albuminuria. Although this patient's serum creatinine level is normal, she has evidence of chronic kidney disease (CKD) based on the presence of albuminuria (urine albumin-creatinine ratio ≥30 mg/g). Albuminuria and uncontrolled blood pressure increase her risk for progression of CKD. Several large randomized controlled trials showed that use of an ACE inhibitor or angiotensin receptor blocker (ARB) can result in decreased progression of albuminuria and CKD, which may include doubling of serum creatinine or progression to end-stage kidney disease, in patients with diabetes and albuminuria.

Although first-line antihypertensive therapy in non-Black patients in the absence of proteinuria includes a thiazide diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB, the American Diabetes Association (ADA) recommends an ACE inhibitor or ARB at the maximum tolerated dose as first-line treatment for hypertension in patients with diabetes and urine albumin-creatinine ratio >300 mg/g; treatment with these drugs should be initiated when the urine albumin-creatinine ratio is ≥30 to 300 mg/g. For this reason, felodipine (a CCB) and *hydrochlorothiazide* (a thiazide diuretic) are not the most appropriate initial therapies for this patient (**Options A-C**).

Initial treatment with two antihypertensive drugs is recommended for patients with stage 2 hypertension and who are >20/10 mm Hg above their target blood pressure. According to the ADA, this patient's target blood pressure is <140/90 mm Hg or <130/80 mm Hg in the presence of atherosclerotic cardiovascular disease or if her 10-year atherosclerotic cardiovascular disease event risk is >15%. Regardless, the patient is not >20/10 mm Hg above her blood pressure target, and the initiation of two antihypertensive drugs is not indicated. However, if this patient's blood pressure is still not controlled to target while receiving the maximum dose of lisinopril, then another class of first-line antihypertensive agents, such as a thiazide diuretic or CCB, should be added.

KEY POINTS

- An ACE inhibitor or angiotensin receptor blocker is the initial treatment of choice for hypertension in patients with diabetes mellitus and albuminuria.
- Use of an ACE inhibitor or angiotensin receptor blocker can result in decreased progression of albuminuria and chronic kidney disease in patients with diabetes mellitus and albuminuria.

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Item 40 Answer: A

Educational Objective: Manage nephrogenic diabetes insipidus.

The most appropriate management is to add amiloride (**Option A**). This patient has polyuria, a serum sodium concentration at the upper limit of normal, and dilute urine, which establish the diagnosis of diabetes insipidus (DI). DI may be secondary to either an inadequate release of antidiuretic hormone (ADH) (central DI) or inadequate action of ADH (nephrogenic DI). Central DI can result from tumors that invade the hypothalamus, infiltrating diseases such as sarcoidosis, or surgical destruction. Nephrogenic DI is often caused by drugs such as lithium. The temporal association with the initiation of lithium in this patient establishes the diagnosis of lithium-induced nephrogenic DI. Up to 40% of patients treated with lithium will develop polydipsia secondary to lithium interfering with the action of ADH. Amiloride is the most appropriate management in this case, as it blocks the epithelial sodium channel in the collecting tubule and prevents the uptake of lithium by these cells. Intracellular lithium appears to decrease the number of aquaporin water channels inserted in the membrane, thereby decreasing water reabsorption causing increased excretion of dilute urine. If amiloride is ineffective and lithium must be continued, the treatment of nephrogenic DI is aimed at decreasing the amount of urine excreted and is best accomplished by limiting solute intake and causing mild volume depletion with the use of a thiazide diuretic. Because the amount of urine excreted daily is dependent on solute intake and minimum urine osmolality, decreasing solute will limit urine volume. By causing mild volume depletion with a thiazide diuretic, more salt and water will be reabsorbed in the proximal tubule and loop of Henle, further decreasing urine output.

Although furosemide (**Option B**) will produce volume depletion, it is not helpful in the treatment of nephrogenic DI. Furosemide blocks the ability to concentrate the urine at the loop of Henle, creating a state of antidiuretic hormone resistance.

Patients with nephrogenic DI will develop increased thirst as their serum sodium increases. Water intake should never be restricted (**Option C**) in patients with nephrogenic DI because it can lead to severe hypernatremia.

Because the treatment of nephrogenic DI is aimed at decreasing solute intake, increasing protein intake (**Option D**) is not appropriate management.

KEY POINTS

- Treatment of lithium-induced nephrogenic diabetes insipidus is best accomplished with amiloride, as it blocks the epithelial sodium channel in the collecting tubule and prevents the uptake of lithium by these cells.
- If amiloride is ineffective in treating lithium-induced nephrogenic diabetes insipidus and lithium must be continued, treatment is aimed at limiting solute intake and causing mild volume depletion with the use of a thiazide diuretic.

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Item 41 Answer: D

Educational Objective: Manage gross hematuria in IgA nephropathy.

The most appropriate management is clinical observation (**Option D**). This patient can be reassured that the gross hematuria is related to his underlying IgA nephropathy and will resolve spontaneously. Recurrent gross hematuria, in which the hematuria occurs in the setting of an upper respiratory infection (synpharyngitic hematuria) or after heavy exertion, is a common manifestation of IgA nephropathy in younger patients; it usually portends a benign clinical course with recurrent episodes of gross hematuria without progression to chronic kidney disease. Other predictors of a benign prognosis include a normal serum creatinine concentration and blood pressure as well as minimal proteinuria.

Amoxicillin (**Option A**) would be indicated to treat streptococcal pharyngitis. However, this diagnosis is unlikely in the presence of cough, the absence of pharyngeal exudate and cervical lymphadenopathy, and a negative rapid antigen test.

CT of the abdomen and pelvis (**Option B**) is an appropriate screening test for unexplained gross hematuria, which may be due to the presence of a stone or mass in the kidney or bladder. However, this patient has a known diagnosis of IgA nephropathy and a classic presentation of synpharyngitic hematuria; the gross hematuria is well explained, and imaging is not required.

Glucocorticoid therapy, such as with prednisone (**Option C**), is unnecessary in a mild form of nonprogressive IgA nephropathy. The use of immunosuppression in progressive IgA nephropathy remains controversial: The STOP-IgAN study showed no benefit of glucocorticoid therapy in slowing the decline of kidney function, and the TESTING study was terminated early due to significantly increased risk for adverse events in patients treated with glucocorticoids. Therefore, glucocorticoid therapy is reserved for severe forms of IgA nephropathy deemed high risk for rapid progression to end-stage kidney disease.

KEY POINTS

- In younger patients with IgA nephropathy, recurrent hematuria in the absence of proteinuria usually portends a benign clinical course and treatment is conservative.
- Recurrent gross hematuria, often occurring at the time of an upper respiratory infection or following strenuous exercise, is a common manifestation of IgA nephropathy in younger patients.

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Item 42 Answer: D

Educational Objective: Manage vaccinations in a patient with chronic kidney disease.

The most appropriate additional vaccine to administer at this visit is the pneumococcal conjugate vaccine (**Option D**). Chronic kidney disease (CKD) is an indication for pneumococcal vaccination. Two pneumococcal vaccines are available: the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23). In adults aged 19 to 64 years with CKD, vaccination with both PCV13 and PPSV23 is indicated. For patients who have not yet received either vaccine, a single dose of PCV13 should be given first, followed by a single dose of PPSV23 given at least 8 weeks later. In this patient, a second dose of PPSV23 should also be administered 5 years after the first PPSV23 dose (**Option E**). In addition, patients with CKD and end-stage kidney disease (ESKD) are at increased risk for influenza-related morbidity and mortality and should be strongly encouraged to receive the influenza vaccine annually. Influenza vaccination has been shown to decrease influenza-related mortality and decrease hospitalization for acute coronary syndrome and heart failure in patients who are vaccinated.

Patients with CKD and ESKD should receive vaccines for hepatitis A or herpes zoster (shingles) (**Options A, C**) and others (for example, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) according to the same guidelines as the general population based on age (>50 years) for the herpes zoster vaccine and hepatitis A vaccine for upcoming travel to endemic areas, and for adults at risk for hepatitis A virus (HAV) infection or severe disease from HAV infection and for adults requesting protection against HAV without acknowledgment of a risk factor.

Patients with ESKD who are receiving hemodialysis and blood transfusions are at increased risk for exposure to blood-borne viruses. Hepatitis B vaccination (**Option B**) is indicated for patients with CKD who are not already immune. For patients on hemodialysis, the vaccine should be administered as part of the infection control program at the dialysis center. Patients with ESKD require a higher dose of vaccine to enhance the likelihood of immune response. Serology indicates that this patient is immune to hepatitis B; therefore, vaccination is not indicated.

KEY POINTS

- Patients with chronic kidney disease and end-stage kidney disease or on hemodialysis should receive both pneumococcal vaccines.
- Patients with chronic kidney disease and end-stage kidney disease are at increased risk for influenza-related morbidity and mortality and should receive the influenza vaccine annually.

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Item 43 Answer: A

Educational Objective: Diagnose contrast-associated acute tubular necrosis.

The most likely diagnosis is acute tubular necrosis (ATN) (**Option A**) due to contrast-associated nephropathy (CAN). CAN is characterized by an abrupt increase in the serum creatinine level 24 to 48 hours after contrast exposure. This patient's risk factors for CAN include chronic kidney injury, type 2 diabetes mellitus, and a presumptive large volume contrast exposure. Laboratory findings consistent with the diagnosis include a blood urea nitrogen (BUN)-creatinine ratio of 15:1, urine specific gravity of 1.010 (isosthenuria), urine sodium >40 mEq/L (40 mmol/L), and a urine sediment with a few granular casts; notably, pigmented granular casts do not have to be present to diagnose ATN.

Atheroembolic-induced acute kidney injury (**Option B**) after a vascular intervention is characterized by a slow, stuttering rise in the serum creatinine level, often not apparent until several days or weeks after the procedure. It is often accompanied by stigmata of atheroemboli to the lower extremities, including livedo reticularis. In this patient, serum creatinine levels began rising 24 hours after the procedure and he has no skin findings.

Clopidogrel can be a cause of hemolytic uremic syndrome (**Option C**). However, this syndrome is typically characterized by a profound decrease in hemoglobin levels and platelet counts, and a longer exposure to the offending agent would be expected before the full manifestations develop. In this patient, the anemia and thrombocytopenia are modest and nonspecific.

Prerenal acute kidney injury (**Option D**) is unlikely in the absence of physical findings supporting hypovolemia or reduced cardiac output. Additionally, BUN-creatinine ratio >20:1, urine specific gravity >1.020, and a normal microscopic urinalysis or presence of hyaline casts are more typical.

KEY POINT

- Contrast-associated nephropathy is a cause of acute tubular necrosis and is characterized by an increase in the serum creatinine 24 to 48 hours after contrast exposure.

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Item 44 Answer: D

Educational Objective: Treat salicylate toxicity.

The most appropriate treatment is intravenous sodium bicarbonate (**Option D**). This patient has salicylate toxicity related to the ingestion of aspirin and has developed a complex mixed acid-base disorder characterized by respiratory alkalosis, increased anion gap metabolic acidosis, and metabolic

H CONT. alkalosis. Intravenous sodium bicarbonate administration increases urinary elimination of salicylate (with a goal of a urine pH >7.5) and protects the patient from central nervous system (CNS) toxicity. Maintaining the serum pH at 7.50 to 7.55 is essential to avoid CNS accumulation of salicylic acid in the brain. Aspirin (acetylsalicylic acid) is rapidly converted to salicylic acid in the body. Acidosis promotes the influx of salicylic acid into the CNS. Increasing the systemic pH with alkali therapy favors the formation of the ionic form of salicylic acid where it is "trapped" in extracellular fluid. The formation of ionic salicylic acid in extracellular fluid creates a favorable concentration gradient for diffusion of salicylic acid from the CNS to the extracellular fluid. Alkalinization of the urine converts urinary salicylic acid to its ionic form, trapping it in the renal tubule and diminishing the diffusion from the renal tubule back into the systemic circulation.

Acetazolamide (**Option A**) is not indicated in the treatment of salicylate toxicity. Although acetazolamide, a carbonic anhydrase inhibitor, can alkalinize the urine, it does so by reducing bicarbonate reabsorption. The alkaline urine will result in enhanced excretion of salicylic acid; however, the loss of bicarbonate will result in a mild systemic acidosis and will drive salicylate into the CNS.

Hemodialysis (**Option B**) is not indicated for this patient. It is indicated for patients with serum salicylate levels >90 to 100 µg/mL (651-724 µmol/L) with acute intoxication and >60 µg/mL (434.4 µmol/L) in chronic administration, or if there is acute kidney injury, cerebral or pulmonary edema, refractory acidemia, or severe alteration of mental status.

Forced diuresis with administration of intravenous 0.9% saline (**Option C**) has no role in managing salicylate toxicity, as it will not increase elimination of salicylate in the absence of systemic and urinary alkalinization.

KEY POINTS

- Salicylate toxicity related to the ingestion of aspirin commonly manifests as a primary respiratory alkalosis or complex mixed acid-base disorders.
- Intravenous sodium bicarbonate administration is used to treat patients with salicylate toxicity, as it increases urinary elimination of salicylate (with a goal of a urine pH >7.5) and protects the patient from central nervous system toxicity.

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Item 45 Answer: C

Educational Objective: Diagnose lupus nephritis.

Kidney biopsy (**Option C**) is the most appropriate diagnostic test to perform next. The 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus (SLE) include having antinuclear antibody (ANA) positivity at least once as obligatory entry criterion, followed by additive weighted criteria grouped into seven clinical and three immunologic domains. Patients with the entry criteria of a positive ANA, at least one clinical criterion, and having accumulated ≥10 points are classified as having SLE with a sensitivity of 96.1% and specificity of 93.4%. This patient has a positive ANA, acute cutaneous lupus erythematosus, and low serum complement levels (10 total points). The classic pattern of lupus nephritis is an immune complex–mediated glomerulonephritis with a varied pathology that includes six distinct classes of disease. The biopsy is crucial not only to establish the diagnosis but also to indicate which class of lupus nephritis she has, as the approach to treating lupus nephritis is guided by histologic class and the degree of kidney function impairment.

Erythrocyte sedimentation rate (ESR) (**Option A**) measurement can be checked serially alongside other clinical parameters to gauge disease activity. However, an ESR measurement would not help in determining the class of lupus nephritis needed to choose optimal therapy.

This patient may test positive for one or more antibodies on the extractable nuclear antigen (ENA) (**Option B**) panel (e.g., anti-Smith, anti-U1-RNP, anti-Ro/SSA, anti-La/SSB), but this antibody panel test is not required to make a diagnosis of SLE. In addition, the results of an ENA panel are not expected to influence treatment plans compared with those of a kidney biopsy.

The diagnosis of acute cutaneous lupus erythematosus is primarily clinical. A skin biopsy (**Option D**) is indicated when the clinical diagnosis is in doubt. In this case, the appearance of the classic malar rash in the context of positive SLE-associated immunologic findings make a skin biopsy unnecessary. Finally, a skin biopsy would not shed any light on the patient's kidney manifestations or guide therapy for either the patient's skin or kidney disease.

KEY POINT

- Kidney biopsy is the definitive diagnostic test for lupus nephritis and, based on histologic findings, is crucial in determining treatment.

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Item 46 Answer: D

Educational Objective: Prepare a patient for end-stage kidney disease by providing renal replacement therapy education.

This most appropriate management is renal replacement therapy (RRT) education (**Option D**). This patient with slowly progressive chronic kidney disease (CKD) is at borderline stage G3/G4. When estimated glomerular filtration rate (eGFR) is <30 mL/min/1.73 m^2, the patient should be referred for RRT education. It is appropriate to begin the education process for the patient to learn about RRT options, including in-center

and home hemodialysis, peritoneal dialysis, kidney transplantation, and non-dialytic medical management, to make an informed decision in the future. An RRT education session empowers the patient to make decisions regarding venous access or preemptive kidney transplant to ensure a controlled initiation of RRT. It also helps prevents the risk for initiating dialysis emergently. Patients who receive preparatory RRT education before they are diagnosed with end-stage kidney disease are more likely to select a home modality for RRT, be listed for a kidney transplant, or receive a preemptive kidney transplant and may have a mortality benefit compared with patients who do not receive similar education.

Evaluation for arteriovenous fistula (AVF) placement (**Option A**) is indicated after the patient has learned about RRT options and chooses to receive hemodialysis in the future. After this decision, the patient is referred for arm-access evaluation. Patients with suitable anatomy should have AVF placement well in advance of anticipated ESKD to allow adequate maturation of the vein to allow robust blood flow needed for hemodialysis.

For patients amenable to dialysis (**Option B**), studies demonstrate no benefit in starting it in asymptomatic patients or at a specific eGFR cutoff compared with watchful waiting and initiating dialysis for symptoms or metabolic abnormalities that are refractory to medical treatment.

Patients should be referred to a kidney transplant center for evaluation (**Option C**) when the eGFR is 15 to 29 mL/min/1.73 m^2. Early referral is important because preemptive kidney transplants (transplants before needing dialysis) are associated with improved clinical outcomes compared with receiving a transplant after starting dialysis. Early referral also allows adequate time to identify suitable living donors; if no living donor is available, early listing is essential to begin the waiting process for a deceased-donor kidney. Referral for evaluation will be appropriate if this patient selects this mode of RRT following RRT education.

KEY POINT

- Patients with progressive chronic kidney disease and an estimated glomerular filtration rate <30 mL/min/1.73 m^2 should be referred to a renal replacement therapy education program.

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Item 47 Answer: A

Educational Objective: Diagnosis calciphylaxis in end-stage kidney disease.

The most likely diagnosis is calciphylaxis (calcific uremic arteriolopathy) (**Option A**). This patient with dialysis-dependent end-stage kidney disease (ESKD) has developed a painful ulcer on the left calf with central necrosis and a skin biopsy showing vascular calcification. Calciphylaxis develops from pathologic calcifications in the dermal arterioles, leading to thrombosis, ischemia, and necrosis of the overlying skin. It is a painful and often life-threatening complication of ESKD and is associated with a high risk of mortality due to secondary infection and sepsis. Many patients with calciphylaxis have severe secondary hyperparathyroidism and elevated calcium-phosphorous product. However, patients such as this one with normalized serum calcium and phosphate levels are also at risk; calciphylaxis is an increasingly recognized complication of ESKD in the dialysis community. There are no FDA-approved treatments for calciphylaxis. However, calcimimetics are used to suppress parathyroid hormone, and data from a large study show fewer cases of calciphylaxis among treated patients. Sodium thiosulfate, an anti-inflammatory agent, is also routinely used for patients with calciphylaxis.

Leukocytoclastic vasculitis (**Option B**) should be considered in the differential diagnosis of a nonhealing leg ulcer, but patients typically present with palpable purpura, not a rapidly advancing cutaneous ulcer, and the biopsy would show perivenular and intramural inflammatory infiltrates rather than the vascular calcifications seen in this patient.

Venous stasis ulcers (**Option C**), a chronic skin condition associated with other signs of venous insufficiency (edema, varicosities, hyperpigmentation), are irregularly shaped, shallow, and often weep serous fluid. The ulcers are rarely necrotic. The sudden appearance of a necrotic ulcer is not indicative of a venous ulcer.

Although warfarin-related necrosis could cause necrotic skin ulceration (**Option D**), it would be expected to occur when the agent was initiated, often with large loading doses, and would not show calcifications in the underlying vessel walls on biopsy but rather thrombosis.

KEY POINTS

- Calciphylaxis (calcific uremic arteriolopathy) is characterized by calcifications in the dermal arterioles resulting in painful ischemic skin lesions and is an increasingly recognized complication of end-stage kidney disease.
- Many patients with calciphylaxis have severe secondary hyperparathyroidism and elevated calcium-phosphorous product.

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Item 48 Answer: C

Educational Objective: Diagnose fibromuscular dysplasia.

The most appropriate diagnostic test to perform next is renal artery CT angiography (**Option C**). Fibromuscular dysplasia should be considered in this young woman with new-onset hypertension and an abdominal bruit. Fibromuscular dysplasia

is a noninflammatory, nonatherosclerotic form of renovascular disease of unknown etiology that affects medium-sized arteries. Fibromuscular dysplasia typically occurs in young persons, particularly women <35 years of age. The abrupt onset of hypertension in a young patient with a lateralizing abdominal bruit suggests the diagnosis. For patients with suspected renal artery fibromuscular dysplasia, CT angiography (CTA) is the initial imaging modality of choice. Contrast-enhanced magnetic resonance angiography (MRA) is an alternative when CTA is contraindicated. Duplex ultrasound may be used as the first diagnostic procedure in specialized centers with extensive expertise with this imaging modality. Patients with fibromuscular dysplasia are at risk for aneurysm formation and/or dissection, most commonly of the renal, carotid, and intracranial arteries. Patients with fibromuscular dysplasia should undergo at least one-time assessment for intracranial aneurysm with brain CTA or MRA.

A plasma aldosterone concentration/plasma renin activity ratio (**Option A**) is obtained in patients with a clinical suspicion for primary hyperaldosteronism; this patient does not have hypokalemia or a metabolic alkalosis that would raise suspicion for hyperaldosteronism. Furthermore, primary hyperaldosteronism cannot explain the abdominal bruit.

Plasma fractionated metanephrines (**Option B**) are obtained to screen for a pheochromocytoma. The absence of episodic palpitations, headaches, and tachycardia make pheochromocytoma a less likely diagnosis in this patient and it cannot explain the abdominal bruit.

There is no indication to obtain a urine albumin-creatinine ratio (**Option D**), as her urinalysis does not show blood that would raise suspicion for glomerulonephritis, which would be another cause of secondary hypertension.

KEY POINTS

- Fibromuscular dysplasia typically occurs in young persons, particularly women <35 years of age, with the abrupt onset of hypertension.
- Renal artery CT angiography is the most appropriate diagnostic test to evaluate for fibromuscular dysplasia.

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Item 49 Answer: E

Educational Objective: Diagnose type 4 (hyperkalemic distal) renal tubular acidosis.

The most likely cause of this patient's hyperkalemia is type 4 (hyperkalemic distal) renal tubular acidosis (RTA) (**Option E**). Type 4 RTA results from either aldosterone deficiency or resistance. Primary adrenal insufficiency (Addison disease) or hyporeninemic hypoaldosteronism may cause aldosterone deficiency. Hyporeninemic hypoaldosteronism is a more common cause and may occur in the presence of various kidney diseases, most often diabetes mellitus. Aldosterone resistance is seen with tubulointerstitial disease, including urinary obstruction, sickle cell disease, medullary cystic kidney disease, and kidney transplant rejection. Drug-induced type 4 RTA can be caused by numerous drugs that reduce aldosterone production, including ACE inhibitors, angiotensin receptor blockers, heparin, and NSAIDs. Patients with type 4 RTA have a positive urine anion gap ([Urine Sodium + Urine Potassium] – Urine Chloride), indicating a reduced excretion of acid in the form of ammonium and chloride but a urine pH <5.5. Hyperkalemia decreases ammonia production with consequent lower ammonium excretion and therefore results in the positive urine anion gap. Due to the inadequate amount of ammonia available to buffer protons, the few protons that are secreted distally will result in the low urine pH (<5.5). Treatment is focused on correcting the underlying cause if possible.

Nonselective β-blockers such as atenolol (**Option A**) block the β-2-adrenergic facilitation of potassium uptake by the cells. The increase in serum potassium is usually very modest unless β-blockade occurs in the context of a potassium load. β-Blockers do not cause a metabolic acidosis.

Although chronic kidney disease (**Option B**) may result in hyperkalemia and metabolic acidosis, the acidosis does not usually develop until the glomerular filtration rate (GFR) is <40 mL/min/1.73 m^2, and hyperkalemia is usually not present until stage G4 disease (GFR <30 mL/min/1.73 m^2).

Although diarrhea (**Option C**) may be associated with normal anion gap metabolic acidosis, the urine anion gap would be negative; this patient has a positive urine anion gap.

The normal anion gap of type 1 (hypokalemic distal) RTA (**Option D**) results from a distal tubular defect and associated impaired excretion of hydrogen ions by the distal nephron. Although the urine anion gap is generally positive, type 1 RTA is usually associated with hypokalemia and urine pH >5.5, which are not present in this patient.

KEY POINTS

- Diabetes mellitus is a common cause of type 4 (hyperkalemic distal) renal tubular acidosis characterized by hyperkalemia, a normal anion gap metabolic acidosis, and a urine pH <5.5.
- Drug-induced type 4 (hyperkalemic distal) renal tubular acidosis can be caused by ACE inhibitors, angiotensin receptor blockers, heparin, and NSAIDs.

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Item 50 Answer: A

Educational Objective: Treat hypertension in a Black patient with a calcium channel blocker.

In addition to continuing therapeutic lifestyle interventions, the most appropriate treatment for this Black patient is to begin antihypertensive medication treatment with amlodipine (**Option A**), a calcium channel blocker (CCB). Lifestyle

modification (i.e., weight reduction, dietary modification, and increased physical activity) is particularly important in Black Americans for prevention and first-line or adjunctive therapy of hypertension; however, most patients will require the addition of pharmacologic therapy. For adults without additional markers of increased cardiovascular risk, a blood pressure (BP) target of <130/80 mm Hg is reasonable. Data show that, in Black individuals, CCBs as well as thiazide diuretics are more effective in lowering BP and cardiovascular events than renin-angiotensin system (RAS) inhibitors, such as ACE inhibitors, angiotensin receptor blockers (ARBs), and direct renin inhibitors. Therefore, initial antihypertensive medication therapy should include a CCB or thiazide diuretic in Black patients without chronic kidney disease (CKD) or heart failure, such as this patient.

RAS inhibitors, such as lisinopril and losartan (**Options B, C**), are recommended in patients with hypertension, diabetes mellitus, nephropathy, and heart failure, or following a myocardial infarction, regardless of race or ethnicity. For patients with CKD, initial or add-on therapy should include an ACE inhibitor or ARB, especially for those with proteinuria. There is no evidence of CKD in this patient, given the normal serum creatinine level and absence of an elevated urine albumin-creatinine ratio. This patient also has no history of heart failure or recent myocardial infarction that would otherwise be an indication for an ACE inhibitor or ARB.

β-Blockers, such as metoprolol (**Option D**), are recommended as initial or add-on therapy for hypertension in patients with heart failure or following a myocardial infarction, regardless of race or ethnicity. There is inadequate evidence to support the initial use of β-blockers to treat hypertension in the absence of these specific cardiovascular comorbidities. This patient has no history of coronary artery disease or heart failure and has no other compelling cardiovascular indication for treatment with metoprolol.

KEY POINTS

- In Black patients with hypertension, a calcium channel blocker or a thiazide diuretic is the preferred initial agent.
- β-Blockers are not indicated as first-line therapy for hypertension in the absence of a compelling reason such as heart failure or recent myocardial infarction, regardless of race or ethnicity.

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Item 51 Answer: D

Educational Objective: Diagnose acute tubular necrosis due to rhabdomyolysis.

The most likely cause of this patient's findings is rhabdomyolysis (**Option D**) caused by acute muscle injury in the setting of extreme physical exertion. Inadequately conditioned individuals who engage in extreme physical challenges under conditions promoting rapid fluid loss are at risk. Rhabdomyolysis causes acute tubular necrosis (ATN), which is believed to be mediated through a combination of direct toxic effects of myoglobin, associated oxygen-free radical production, and local renal vasoconstriction. Rhabdomyolysis-induced ATN is more likely to occur with serum creatine kinase (CK) levels >5000 U/L. In addition to elevated serum CK and creatinine levels, hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, metabolic acidosis, increased lactate dehydrogenase concentration, and increased aspartate and alanine aminotransferase levels can occur. Urinary findings include fractional excretion of sodium <1% (caused by renal vasoconstriction), myoglobinuria, pigmented (red) granular casts, and a urine dipstick positive for blood with the absence of a significant number of erythrocytes on urine microscopy.

Immune-mediated necrotizing myopathy (**Option A**) typically presents with progressive proximal weakness and an elevated serum CK level; diagnosis is based on muscle biopsy findings of necrotic fibers with limited inflammation. Onset can be triggered by statins, or it may present as a paraneoplastic syndrome. The onset can be acute or slowly progressive but does not cause ATN.

The inflammatory myopathies (**Option B**) commonly present with symmetric proximal muscle weakness without substantial muscle pain or tenderness. Serum CK is almost universally elevated in the inflammatory myopathies and is a marker of muscle damage, but the urinalysis is normal. The onset tends to be insidious and presence of pain or tenderness should prompt considerations of other causes of myopathy.

March hemoglobinuria (**Option C**) develops after physical erythrocyte destruction in the soles of the feet in response to long-distance running or marching. Both hematuria and hemoglobinuria due to hemolysis may result in reddish-brown urine. Serum CK levels in these patients will not be elevated.

KEY POINTS

- Rhabdomyolysis is associated with elevated serum creatinine and creatine kinase levels and may be associated with hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, increased lactate dehydrogenase concentration, and metabolic acidosis.
- In patients with acute tubular necrosis caused by rhabdomyolysis, urinary sediment is characterized by amorphous tubular debris, including heavily pigmented granular casts.

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Item 52 Answer: B

Educational Objective: Treat stage 1 hypertension with nonpharmacologic and pharmacologic therapy.

The most appropriate additional management is to start amlodipine (**Option B**). Adults with stage 1 hypertension (systolic blood pressure [SBP] of 130–139 mm Hg or diastolic blood pressure [DBP] of 80–89 mm Hg) who have an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) event risk of ≥10% should be managed initially with a combination of nonpharmacologic and antihypertensive drug therapy and have a repeat BP evaluation in 1 month. Initial pharmacologic therapy for Black patients in the absence of heart failure or chronic kidney disease is either a calcium channel blocker (CCB), such as amlodipine, or a thiazide diuretic.

Adults with an elevated BP (SBP of 120–129 mm Hg and a DBP <80 mm Hg) or stage 1 hypertension who have an estimated 10-year ASCVD risk <10% should be managed with nonpharmacologic therapy and have a repeat BP evaluation within 3 to 6 months (**Option A**). Lifestyle modifications (weight loss, heart-healthy diet, sodium reduction, potassium supplementation, increased physical activity) and management of cardiovascular risk factors (tobacco use, diabetes mellitus, hyperlipidemia) should be addressed in all patients with hypertension. This patient is at increased risk for an ASCVD event, and treatment with both nonpharmacologic and pharmacologic therapy is indicated.

Combination therapy with two-first line drugs (**Option C**) (with the exception of an ACE inhibitor and ARB combination) that act by different mechanisms is indicated for patients with stage 2 hypertension (>140/90 mm Hg). Combined pharmacologic therapy is not indicated in this patient with stage 1 hypertension.

ACE inhibitors such as lisinopril (**Option D**), angiotensin receptor blockers (ARBs) such as losartan, thiazide diuretics such as chlorthalidone, and CCBs are all first-line antihypertensive medication classes. However, in the absence of heart failure or chronic kidney disease, CCBs or thiazide diuretics are preferred in Black patients because they are the most efficacious.

KEY POINTS

- Adults with stage 1 hypertension who have an estimated 10-year atherosclerotic cardiovascular disease event risk of <10% should be managed initially with nonpharmacologic therapy.
- Adults with stage 1 hypertension who have an estimated 10-year atherosclerotic cardiovascular disease event risk of ≥10% should be managed initially with nonpharmacologic and antihypertensive drug therapy.

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Item 53 Answer: A

Educational Objective: Manage chronic hypertension before conception.

The most appropriate management is to discontinue the ACE inhibitor ramipril (**Option A**) in this patient who is planning pregnancy. Renin-angiotensin system blocking agents, such as ACE inhibitors, angiotensin receptor blockers (ARBs), and direct renin inhibitors, are contraindicated in pregnancy and should be discontinued before conception. Exposure during the second and third trimesters of pregnancy has been associated with neonatal kidney failure and death.

In pregnant patients with chronic hypertension, the 2019 American College of Obstetricians and Gynecologists (ACOG) guidelines recommend a systolic blood pressure during pregnancy of 120 to <160 mm Hg and a diastolic pressure of 80 to <110 mm Hg. In the setting of comorbidities or underlying impaired kidney function, treating at lower blood pressure thresholds may be appropriate. This patient's blood pressure is well within this range on treatment, and her blood pressure would be expected to decline during pregnancy. Therefore, monitoring her blood pressure after discontinuation of ramipril without the initiation of a replacement drug is a reasonable approach. If her blood pressure increases beyond the target range during pregnancy, initiation of a drug that is safe in pregnancy is recommended. In that event, first-line therapy includes methyldopa, labetalol, and nifedipine.

Pregnant patients with acute and severe hypertension have been successfully and safely treated with parenteral hydralazine. There is less experience in its use as a routine oral antihypertensive drug in pregnant women with chronic hypertension. Hydralazine is an unlikely first-line drug (**Option B**) for pregnant women needing antihypertensive treatment because it causes reflex tachycardia, often necessitating combination with a β-blocking drug, and results in fluid retention, often requiring the addition of a diuretic.

Mineralocorticoid receptor antagonists such as spironolactone (**Option C**) and eplerenone also block the renin-angiotensin system. This class of drug is often used in patients with hyperaldosteronism and resistant hypertension, but it has not been shown to be safe in pregnancy.

Not discontinuing the ramipril (**Option D**) in this patient at this point in time is unsafe. The safest approach is to discontinue any inhibitor of the renin-angiotensin system before conception.

KEY POINTS

- Renin-angiotensin system blocking agents (ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors, and mineralocorticoid receptor antagonists) are contraindicated in pregnancy and should be discontinued before conception.
- Chronic hypertension guidelines for pregnant women recommend a systolic blood pressure of 120 to <160 mm Hg and a diastolic pressure of 80 to <110 mm Hg.

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Item 54 Answer: C

Educational Objective: Treat uric acid kidney stones.

The most appropriate treatment is potassium citrate (**Option C**). Acute management of symptomatic nephrolithiasis is aimed at pain management and facilitation of stone passage. Pain can be relieved by NSAIDs and opioids as needed. Stone passage decreases with increasing size. Only 50% of stones >6 mm will pass, and stones >10 mm are extremely unlikely to pass spontaneously. This patient most likely has a uric acid kidney stone. On helical CT scan, the density of the stone, as measured by Hounsfield units, is suggestive of uric acid. Patients with a uric acid kidney stone will have an acidic urine pH, as seen in this patient (pH 5.0). Uric acid stones are also more common in individuals with metabolic syndrome, as seen in this patient. The most effective treatment for uric acid stones is to alkalinize the urine, as uric acid is readily soluble in alkaline urine. If the urine pH is increased to 6.5 to 7.0, more than 90% of uric acid will be converted to soluble urate salts, dissolving the stone. Administration of potassium citrate at a dose of 40 to 80 mEq/d will effectively alkalinize the urine and reduce the size of the stone, allowing it to rapidly transit to the bladder.

Allopurinol (**Option A**) should be reserved to treat patients with gout and/or recurrent uric acid kidney stones that are unresponsive to alkalinization and increased fluid intake, neither of which applies to this patient.

Lithotripsy (**Option B**) is an appropriate treatment for kidney stones >6 mm that are unlikely to pass. However, for this patient, the 5-mm stone will likely pass, especially if the urine pH is increased to 6.5 to 7.0.

The data concerning the use of tamsulosin (**Option D**) to facilitate stone passage are controversial. But because there are few adverse effects attributed to this medication, many experts recommend its use. In the case of uric acid stones, urinary alkalinization with the use of potassium citrate is a more effective treatment.

KEY POINT

- The most effective treatment to facilitate the passage of uric acid stones is urinary alkalinization with potassium citrate.

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Item 55 Answer: D

Educational Objective: Identify drugs as a nonglomerular cause of an increase in serum creatinine level.

No further management (**Option D**) is indicated for this patient. Some medications (such as cimetidine, trimethoprim, cobicistat, dolutegravir, and bictegravir) reduce proximal tubule secretion of creatinine, resulting in increases in serum creatinine that are nonprogressive; they do not affect glomerular filtration rate (GFR). This patient's antiretroviral regimen was changed to include dolutegravir 6 weeks earlier. Slight increases in serum creatinine of 0.2 mg/dL to 0.3 mg/dL (17.7-26.5 µmol/L) may occur. This is more pronounced in patients with chronic kidney disease (CKD), in which creatinine secretion contributes proportionately more to creatinine clearance. In patients with CKD who are taking the integrase inhibitors dolutegravir or bictegravir, the non-nucleoside reverse transcriptase inhibitor rilpivirine, or the pharmacokinetic enhancer (CYP3A inhibitor) cobicistat, serum creatinine elevations are nonprogressive and will remain stable within 1 to 2 weeks of initiation. Therefore, in the absence of other signs of kidney disease (hematuria, pyuria, or increasing proteinuria), and with a serum creatinine that has remained unchanged since the patient's 4-week assessment, no further evaluation is necessary. In this case, measuring the patient's serum cystatin C level could be a helpful confirmatory test, because the level is not affected by these medications.

Discontinuation of combined lisinopril-hydrochlorothiazide (**Option A**) is not necessary. This patient has been taking her current antihypertensive combination for 6 years, and it is unlikely to have caused this acute increase in serum creatinine; the hemodynamic effects of ACE inhibitors on glomerular filtration occur within days of initiation.

A 24-hour urine creatinine clearance (**Option B**) will be decreased in this case (due to drug-related lower creatinine secretion) and will not provide additional diagnostic information.

Returning to the prior antiretroviral regimen (**Option C**) is not indicated, as the effects of dolutegravir on the patient's serum creatinine level does not indicate GFR decline.

KEY POINT

- Some medications (such as cimetidine, trimethoprim, cobicistat, dolutegravir, and bictegravir) reduce proximal tubule secretion of creatinine, resulting in increases in serum creatinine.

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Item 56 Answer: A

Educational Objective: Treat difficult-to-control hypertension by adding a diuretic.

The most appropriate next step in management is to add chlorthalidone, a thiazide diuretic (**Option A**). Resistant hypertension is defined as blood pressure (BP) that remains above goal despite concurrent use of three antihypertensive agents of different classes, or BP at goal but requiring four or more medications. One of these medications must be a diuretic. Suboptimal antihypertensive therapy in patients

with difficult-to-control hypertension is frequently the result of not including a diuretic agent, which ensures that extracellular volume expansion is prevented or treated. Therefore, before a diagnosis of resistant hypertension is made or evaluation is initiated for secondary causes of hypertension, the patient should be treated with an appropriate diuretic medication, with attention to effective dose and dosing frequency. Although hydrochlorothiazide is the most commonly used thiazide diuretic, chlorthalidone has a longer half-life, which allows once-daily dosing; some evidence from trials suggests efficacy in reducing cardiovascular events.

Obtaining a plasma aldosterone concentration/plasma renin activity ratio (**Option B**) is not indicated at this time, as there is no clinical suspicion for primary hyperaldosteronism such as resistant hypertension, hypokalemia, incidentally discovered adrenal mass, family history of early-onset hypertension, or stroke at age <40 years. This patient does not have hypokalemia or a metabolic alkalosis to raise suspicion for hyperaldosteronism.

Testing for plasma fractionated metanephrines (**Option C**), which screens for a pheochromocytoma, is not indicated. The following characteristics raise clinical suspicion for pheochromocytoma: resistant hypertension; new-onset hypertension or onset at a young age; paroxysmal hypertension; episodic tachycardia, headaches, and sweating; history of familial syndromes; adrenal adenoma found incidentally on imaging with or without hypertension; or pressor response during invasive procedures or anesthesia. The patient has none of these indications for testing.

Obtaining renal artery imaging (**Option D**) is not indicated, as there is no clinical suspicion for renal artery stenosis, which includes the onset of severe hypertension in patients >55 years of age, recurrent flash pulmonary edema, refractory heart failure, or acute kidney injury after initiation of an ACE inhibitor or angiotensin receptor blocker.

KEY POINT

- Resistant hypertension is blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, or blood pressure at goal but requiring four or more medications; one of these medications must be a diuretic.

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Item 57 Answer: D

Educational Objective: Identify urea diuresis as the cause of hypernatremia.

The most likely cause of this patient's hypernatremia is urea diuresis (**Option D**). This patient has polyuria, which can be categorized as a water diuresis or a solute diuresis based on the urine osmolality. In osmotic diuresis, urine osmolality is usually between 300 and 600 mOsm/kg H_2O. This patent's urine osmolality is elevated (560 mOsm/kg H_2O), likely indicating a solute diuresis. This can be further categorized as an electrolyte diuresis or a nonelectrolyte diuresis. Because the total electrolyte in her urine comprises <50% of the urine osmolality [2 × (Urine Sodium + Urine Potassium)], this patient is having a solute diuresis. She takes dexamethasone, which, due to its catabolic effect, has increased the blood urea nitrogen, resulting in a urea diuresis with subsequent loss of water. This can be confirmed by measuring the urine urea concentration. Treatment for this patient would be to either increase her water intake or decrease the dexamethasone dose.

Although diabetes insipidus (**Option A**) may occur in patients who have undergone neurosurgery, this patient's increased urine osmolality is inconsistent with diabetes insipidus.

An electrolyte diuresis (**Option B**) is typically caused by intravenous administration of a large volume of 0.9% saline or after relief of bilateral urinary tract obstruction, resulting in polyuria. When urine output increases, a common response is to increase the intravenous infusion rate, which further increases the sodium load and promotes urine output and causes an unending spiral; in this case, the urine electrolyte concentration cannot explain the ongoing diuresis. In addition, although an increase in sodium intake will cause polyuria, unless the sodium load is hypertonic, it will not result in hypernatremia.

Dexamethasone can increase serum glucose levels. Although this patient's serum glucose level is elevated, it is below the renal threshold (approximately 180 mg/dL [10 mmol/L]) for complete reabsorption. Therefore, a glucose diuresis (**Option C**) is not responsible for either the patient's polyuria or hypernatremia.

KEY POINTS

- Polyuria is caused by either a water diuresis (dilute urine) or a solute diuresis (urine osmolality, 300-600 mOsm/kg H_2O).
- Polyuria caused by an osmotic diuresis is caused by either an electrolyte diuresis or a nonelectrolyte diuresis (e.g., urea, glucose).

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Item 58 Answer: D

Educational Objective: Evaluate a kidney transplant recipient for side effects of immunosuppressive therapy.

Tacrolimus (**Option D**) is the most likely medication responsible for this patient's tremor. Immunosuppressive medications allow successful kidney transplantation but have numerous side effects that should be considered when patients on these medications present with new symptoms. Long-term maintenance therapy for most kidney transplant recipients includes a combination of calcineurin inhibitors (tacrolimus

or cyclosporine), antimetabolites (mycophenolate mofetil or azathioprine), and glucocorticoids. Tremor is an oscillatory movement of a body part that is classified based on its presence at rest or with action. Tremor is a side effect of calcineurin inhibitors and is most common with tacrolimus. Calcineurin-induced tremor is bilateral and may affect the hands and feet. Tacrolimus tremor is activated by action, but in about 50% of cases the tremor can be classified as both an action and resting tremor. The tremor is associated with elevated drug levels and may be most pronounced when drug levels peak following a dose. This patient's tacrolimus trough measurement should be checked, as treatment interventions include dose reduction if permissible, conversion to long-acting formulations, addition of a β-blocker, or conversion to an alternate agent if the tremor is debilitating and unresponsive to other interventions. These adjustments should be made in conjunction with the patient's nephrologist or transplant program. Other side effects of calcineurin inhibitors include new-onset type 2 diabetes mellitus, decreased glomerular filtration rate, hypertension, dyslipidemia, and gingival hyperplasia.

Metoprolol (**Option A**) is not causing, and may be useful in treating, this patient's tacrolimus-related tremor.

Side effects of mycophenolate mofetil (**Option B**) include nausea, vomiting, diarrhea, leukopenia, and anemia, but not tremor.

Although glucocorticoids such as prednisone (**Option C**) cause a myriad of effects that may include psychological distress and jumpiness, they do not cause tremor. Other side effects associated with glucocorticoids include hypertension, edema, new-onset type 2 diabetes, osteoporosis, and osteonecrosis.

KEY POINT

- Calcineurin inhibitor side effects include tremor, new-onset type 2 diabetes mellitus, decreased glomerular filtration rate, hypertension, dyslipidemia, and gingival hyperplasia.

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Item 59 Answer: A

Educational Objective: Diagnose abdominal compartment syndrome.

The most appropriate diagnostic test to perform next is bladder pressure measurement (**Option A**). This patient may have abdominal compartment syndrome (ACS), which is defined as a sustained intra-abdominal pressure >20 mm Hg that is associated with at least one organ dysfunction. The diagnosis of ACS should be considered in the setting of abdominal surgery, trauma, intra-abdominal bleeding, ascites, bowel obstruction, ileus, or pancreatitis. It can also be caused by a capillary leak in the setting of sepsis and massive fluid resuscitation. The diagnosis of ACS can be confirmed through measurement of bladder pressure using an indwelling catheter as a surrogate for intra-abdominal pressure measurement. Appropriate treatment includes surgical decompression of the abdominal compartment.

CT urography (**Option B**) is the diagnostic test of choice for patients with unexplained hematuria and allows characterization of kidney tumors and cysts. MRI with contrast is an alternative for evaluation of kidney masses and cysts when CT cannot be performed. These imaging tests would not be useful in this patient with acute kidney injury.

Indications for kidney biopsy (**Option C**) include glomerular hematuria, severely increased albuminuria, acute or chronic kidney disease of unclear cause (in the absence of atrophic kidneys), and kidney transplant dysfunction or monitoring. Bladder pressure measurement is indicated as the next test because it is the most likely to provide a diagnosis, obviating the need for additional testing.

Kidney ultrasonography (**Option D**) is helpful to exclude obstruction, but new bilateral ureteral obstruction is not strongly suspected in this patient and the placement of a bladder catheter rules out acute urethral obstruction.

KEY POINTS

- Abdominal compartment syndrome is defined as a sustained intra-abdominal pressure >20 mm Hg that is associated with at least one organ dysfunction.
- The diagnosis of abdominal compartment syndrome can be confirmed through measurement of bladder pressure via a bladder catheter as a surrogate for intra-abdominal pressure measurement.

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Item 60 Answer: D

Educational Objective: Treat isovolemic hypernatremia.

The most appropriate treatment for this patient's hypernatremia is administration of water via nasogastric tube (**Option D**). Hyperglycemic hyperosmolar syndrome (HHS), an acute complication of type 2 diabetes mellitus, manifests as extreme hyperglycemia and must be treated early and aggressively to avoid life-threatening consequences from dehydration and electrolyte abnormalities. Extreme glucosuria causes an osmotic diuresis and severe volume depletion, which may be exacerbated by gastrointestinal losses of volume and electrolytes. The condition may progress to lethargy, obtundation, and death. Treatment includes vigorous hydration and insulin. This patient became hypernatremic because of water loss during glucose-induced osmotic diuresis. Treatment of his hyperglycemia with insulin caused a decrease in extracellular osmolality, causing water to move into cells. For

H CONT. every 100-mg/dL (5.6-mmol/L) decrease in serum glucose, serum sodium will increase by approximately 2.0 mEq/L (2.0 mmol/L). This patient's water deficit is approximately 4500 mL, making administration of water the most appropriate treatment. Because this patient is confused, administration of water through nasogastric tube is the best approach; otherwise, the patient could receive water orally. Although decreases of serum sodium up to 1.0 mEq/L (1.0 mmol/L) per hour do not appear to have adverse effects, most authorities recommend decreasing serum sodium by no more than 10 mEq/L (10 mmol/L) daily. Because of ongoing water losses, the calculated rate of correction will be somewhat lower than the actual rate.

Administration of 5% dextrose (**Option A**) is as effective as water in treating hypernatremia. However, this patient has hyperglycemia, and administration of a glucose-containing solution may worsen it as well as increase free water losses by inducing an osmotic diuresis.

Although 0.45% normal saline (**Option B**) is hypotonic and will correct this patient's elevated serum sodium, a minimum of 9 liters is necessary to decrease serum sodium into the normal range.

The use of 0.9% saline (sodium concentration = 154 mEq/L [154 mmol/L]) (**Option C**) will not improve this patient's hypernatremia. Furthermore, it will worsen his already elevated blood pressure and further exacerbate his hyperchloremic metabolic acidosis.

KEY POINTS

- The treatment of isovolemic hypernatremia is water, preferably orally or by nasogastric tube if the patient is incapable of drinking.
- The rate of correction of serum sodium for hypernatremia should be <10 mEq/L (10 mmol/L) daily.

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Item 61 Answer: B

Educational Objective: Treat hypertension with a loop diuretic in advanced chronic kidney disease.

The most appropriate additional treatment for this patient's antihypertensive medication regimen is furosemide (**Option B**). ACE inhibitors or angiotensin receptor blockers (ARBs) are first-line medications for patients with advanced chronic kidney disease (CKD) or proteinuric CKD. Calcium channel blockers reduce albuminuria and slow the decline in kidney function but should be combined with an ACE inhibitor or ARB. Diuretics are the backbone of hypertension management in patients with CKD because of increased extracellular volume. This patient has an elevated blood pressure not controlled to a target goal of <130/80 mm Hg in the setting of stage G4 CKD and evidence of a sodium-retentive state based on the presence of jugular venous distention and lower extremity edema. A thiazide diuretic will unlikely be effective, as her estimated glomerular filtration rate is <30 mL/min/1.73 m^2. Therefore, a loop diuretic, such as furosemide, two or three times daily, is indicated for management of this patient's hypertension. Suboptimal blood pressure control in patients with sodium-retentive, edematous conditions, such as advanced CKD, heart failure, and cirrhosis, is frequently the result of not including a diuretic, which ensures that extracellular volume expansion is prevented or treated.

Without a compelling indication such as heart failure or recent myocardial infarction, the addition of a β-blocker such as carvedilol (**Option A**) to this patient's treatment regimen is not appropriate. Additionally, a β-blocker will not reduce this patient's expanded extracellular volume, thus limiting its ability to reduce the blood pressure.

Similarly, hydralazine (**Option C**) is not indicated at this time because it will likely increase the patient's already expanded extracellular volume, resulting in inadequate blood pressure control.

Although the patient has CKD and albuminuria, adding lisinopril (**Option D**), an ACE inhibitor, to the patient's antihypertensive medication regimen, which already includes losartan, an ARB, is not the appropriate treatment. Combination therapy with an ACE inhibitor and ARB may result in adverse events, such as acute kidney injury and hyperkalemia, and does not improve cardiovascular outcomes compared with treatment with an ACE inhibitor or ARB alone.

KEY POINT

- A loop diuretic such as furosemide is indicated for treating hypertension in patients with advanced chronic kidney disease.

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Item 62 Answer: A

H

Educational Objective: Manage venous access for a patient with chronic kidney disease.

Internal jugular vein insertion of a central venous catheter is the most appropriate method of venous access for this patient (**Option A**). Patients with advanced chronic kidney disease (CKD) may ultimately require renal replacement therapy. Arteriovenous fistula (AVF) placement is the safest and most enduring option for vascular access. AVFs have superior clinical outcomes compared with arteriovenous grafts. Protecting the veins of the nondominant arm is of paramount importance for the future success of a functioning AVF and involves limiting phlebotomy and intravenous catheters in that arm.

Peripherally inserted central catheters (PICCs) (**Options B, C**) are long catheters that are inserted peripherally and terminate in the central veins. PICCs are popular because of their ease of insertion and use. PICC lines can lead to significant trauma and venous stenosis in the veins that may be

H CONT. used for AVF creation. This could impair blood flow through the fistula, impair maturation, and even lead to primary nonfunctioning of the hemodialysis access. Data demonstrate that PICC lines in either arm, placed before or after initiation of hemodialysis, are independently associated with a 15% to 20% lower likelihood of transition to any working fistula or graft. The long-term use of PICC lines is also associated with an increased risk for death. The American Society of Nephrology recommends that PICC line catheters should be avoided in patients with an estimated glomerular filtration rate <60 mL/min/1.73 m^2.

Avoidance of subclavian venous catheters (**Option D**) helps limit subclavian stenosis, which can impair the proper functioning of an arteriovenous access used for dialysis. Although central lines inserted through the internal jugular vein are associated with central venous stenosis, a central line is a better alternative than a PICC or subclavian insertion of a central venous catheter; central lines are not inserted into a peripheral vein, which would be used for the creation of a hemodialysis site, and utilize a vessel not as prone to stenosis as the subclavian vein.

KEY POINT

- The American Society of Nephrology recommends that peripherally inserted central catheter line catheters should be avoided in patients with an estimated glomerular filtration rate <60 mL/min/1.73 m^2.

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Item 63 Answer: B

Educational Objective: Diagnose anti-glomerular basement membrane antibody disease.

The most appropriate serologic test to perform next is measurement of anti-glomerular basement membrane (anti-GBM) antibodies (**Option B**). This patient has rapidly progressive glomerulonephritis (RPGN), defined as an acute and steep rise in serum creatinine accompanied by hematuria and proteinuria. The differential diagnosis for RPGN is divided histologically into three patterns on immunofluorescence microscopy of the kidney biopsy: pauci-immune staining (ANCA-mediated glomerulonephritis), linear staining (anti-GBM glomerulonephritis), and granular staining (lupus nephritis). This patient has RPGN and a kidney biopsy showing linear staining, which is seen in anti-GBM antibody disease. Lung involvement (Goodpasture syndrome) occurs in >50% of patients with anti-GBM antibody disease; hemoptysis can be a presenting symptom, although shortness of breath or cough should also raise suspicion for a pulmonary-renal syndrome even in the absence of hemoptysis. Testing for anti-GBM antibodies is required as the next step in management to confirm diagnosis. For this patient, anti-GBM antibody titers would also be used to monitor treatment response. Up to one in three patients with anti-GBM antibody disease will have positive ANCA serologies, usually antimyeloperoxidase (MPO) antibodies, which can affect prognosis. Combined seropositivity is most commonly seen in patients with anti-GBM antibody disease who are older women. Therefore, it is appropriate to test for p-ANCA/anti-MPO and c-ANCA/antiproteinase 3 antibodies. Successful treatment, which typically includes glucocorticoids, plasmapheresis, and cyclophosphamide, will eradicate the patient's serum anti-GBM antibody titer.

Testing for anti-double-stranded DNA antibodies (**Option A**) is not required in this patient, as his antinuclear antibody test is negative and his kidney biopsy shows no granular staining suggestive of lupus nephritis.

Anti-phospholipase A2 receptor antibodies (**Option C**) can be checked in patients suspected of having primary membranous nephropathy, which typically presents with the nephrotic syndrome and preserved kidney function. The findings of erythrocytes and erythrocyte casts also argue against primary membranous nephropathy.

IgA nephropathy (IgAN) can present with any of the manifestations of the nephritic syndrome. Diagnosis can only be made when kidney biopsy shows dominant mesangial immune deposits of IgA with C3, and occasionally IgG or IgM. Circulating IgA levels (**Option D**) are not diagnostically useful, nor can they be reliably correlated with disease activity and should not be obtained. This patient's kidney biopsy shows linear staining, which is not consistent with IgAN.

KEY POINTS

- Anti-glomerular basement membrane antibody disease is characterized by necrotizing and crescentic glomerulonephritis with linear staining for IgG on immunofluorescence.
- Measurement of anti-glomerular basement membrane (anti-GBM) antibodies confirm the diagnosis of anti-GBM antibody disease and are used to monitor response to treatment.

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Item 64 Answer: A

Educational Objective: Diagnose IgG4-related disease.

The most likely diagnosis is IgG4-related disease (IgG4-RD) (**Option A**), which is typically characterized by infiltration and tumefaction of the affected tissue with resultant organ enlargement, fibrosis, and dysfunction. Patients commonly present with a sentinel organ enlargement, but careful evaluation often reveals more extensive disease. Some common presentations of IgG4-RD include idiopathic pancreatitis, sclerosing cholangitis, bilateral salivary and/or lacrimal gland enlargement, retroperitoneal fibrosis, orbital pseudotumor, or proptosis. Diagnosis is made by tissue biopsy, which

demonstrates a dense lymphoplasmacytic infiltrate, CD4-positive T cells and plasma cells in germinal centers, IgG4-staining plasma cells, storiform fibrosis, obliterative phlebitis or arteritis, and tissue eosinophilia. IgG4 levels are elevated in the serum in 70% to 80% of patients; therefore, a normal serum IgG4 level does not rule out the disease. Initial treatment is prednisone. In this patient, clues to the underlying diagnosis are the presence of idiopathic pancreatitis and large kidney size for a patient with chronic kidney disease. Kidney involvement of IgG4-RD typically manifests as chronic interstitial nephritis (CIN) with fibrosis; plasma cells typically stain positive for IgG4.

Sarcoidosis (**Option B**) is most commonly characterized by noncaseating granulomas and CIN changes on biopsy. Sarcoidosis does not explain this patient's episodes of idiopathic pancreatitis or the lymphoplasmacytic cell infiltrate on kidney biopsy.

Systemic lupus erythematosus (SLE) (**Option C**) may present with CIN. However, SLE more frequently manifests in the kidney as acute glomerular disease and is not associated with pancreatitis or lymphoplasmacytic cell infiltrate on kidney biopsy.

Tubulointerstitial nephritis with uveitis (TINU) (**Option D**) is a distinct syndrome of acute interstitial nephritis with features of uveitis and may be accompanied by various autoantibodies and hypocomplementemia. Most patients with TINU are adolescents and young women. This patient's clinical syndrome is not consistent with TINU.

KEY POINTS

- Patients with IgG4-related disease commonly present with a sentinel organ enlargement and dysfunction, but careful evaluation often reveals more extensive disease.
- Kidney involvement of IgG4-related disease typically manifests as chronic interstitial nephritis with fibrosis and dense lymphoplasmacytic infiltrate.

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Item 65 Answer: B

Educational Objective: Identify multiple myeloma as a cause of isotonic hyponatremia.

The most likely cause of this patient's hyponatremia is multiple myeloma (**Option B**). Results of this patient's laboratory studies, including elevated serum calcium, anemia, and elevated total protein and low albumin suggesting an increased gamma globulin fraction, support the diagnosis of multiple myeloma. The key finding, however, is that the patient has a normal measured serum osmolality in the context of hyponatremia. When evaluating a patient with hyponatremia, the first step is to measure serum osmolality. In this patient, the serum osmolality is normal, and thus he has isotonic hyponatremia. Isotonic hyponatremia (serum osmolality, 275-295 mOsm/kg H_2O) is a laboratory artifact caused by the method by which serum sodium is measured. Plasma is divided into a water phase (93%), in which the sodium is dissolved, and a solid phase (7%), which consists of lipids and proteins. If the solid phase is increased by an increase in proteins, such as those found in multiple myeloma or severe elevations in serum triglycerides, there is a decrease in the water phase (i.e., from 93% to 80%). Most laboratories use a diluting electrode in which there is a tenfold dilution of the specimen when measuring electrolytes. With a decrease in the aqueous phase, the dilution is no longer 1:10, but even greater, resulting in a spurious value for sodium.

Hypercalcemia (**Option A**) can cause polyuria secondary to nephrogenic diabetes insipidus, which would increase the sodium concentration, not lower it, as seen in this patient.

Because the kidney requires solute to excrete water, a decrease in solute intake (**Option C**), which occurs in potomania (excessive beer drinking) or in individuals with starvation, the kidney's ability to excrete water is reduced and can result in hyponatremia without excessive water intake. In these cases, urine osmolality would be <100 mOsm/kg H_2O.

In psychogenic polydipsia (**Option D**), excess water intake exceeds the kidney's ability to excrete water through the urine, and urine osmolality would likely be <100 mOsm/kg H_2O.

In the syndrome of inappropriate antidiuretic hormone (SIADH) secretion (**Option E**), the measured serum osmolality is always low, unlike that seen in this patient. Furthermore, patients with SIADH have hypo-osmolar hyponatremia.

KEY POINTS

- The first step in evaluating a patient with hyponatremia is to measure serum osmolality.
- Isotonic hyponatremia is a laboratory artifact caused by increased plasma concentrations of lipids or proteins.

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Item 66 Answer: D

Educational Objective: Diagnose surreptitious vomiting as a cause of metabolic alkalosis.

The most likely cause of this patient's metabolic alkalosis is surreptitious vomiting (**Option D**). Metabolic alkalosis is diagnosed by an elevation in serum bicarbonate concentration and elevated serum pH. This disorder is caused by either a loss of acid or administration or retention of bicarbonate. Conditions that contribute to the maintenance of metabolic alkalosis include volume contraction, ineffective arterial blood volume, hypokalemia, chloride depletion, and decreased glomerular

filtration. Laboratory evaluation of metabolic alkalosis is based on urine chloride concentration. Metabolic alkalosis is considered saline responsive when associated with true hypovolemia and responds to correction of the volume deficit with isotonic saline. Saline-responsive metabolic alkalosis presents with a low urine chloride of <15 mEq/L (15 mmol/L); the most common causes are vomiting, nasogastric suction, and diuretic use. Hypokalemia in these circumstances occur secondarily due to aldosterone elevation and cation loss as the kidney attempts to lose bicarbonate. Although these patients are usually hypovolemic or normovolemic (with normal or low blood pressures), patients with preexisting chronic hypertension may present with high to normal blood pressures.

Bartter syndrome (**Option A**) and Gitelman syndrome are autosomal recessive genetic disorders of renal sodium and chloride transporters that clinically mimic loop diuretic and thiazide diuretic use, respectively. Both syndromes present with hypokalemic alkalosis with urine chloride (>15 mEq/L [15 mmol/L]); therefore, neither syndrome is the diagnosis in this case.

The presence of hypertension, metabolic alkalosis, and hypokalemia suggests elevated aldosterone states such as Cushing syndrome and primary hyperaldosteronism (**Options B, C**). However, the presence of a low urine chloride (<15 mEq/L [15 mmol/L]) in this patient rules out these diagnoses. Patients with high urine chloride (>15 mEq/L [15 mmol/L]), elevated blood pressure, and hypokalemia who do not appear to be overtly volume overloaded should be evaluated for a mineralocorticoid excess disorder (saline-resistant metabolic alkalosis) such as Cushing syndrome and primary hyperaldosteronism.

KEY POINTS

- Saline-responsive metabolic alkalosis presents with a low urine chloride of <15 mEq/L (15 mmol/L); the most common causes are vomiting, nasogastric suction, and diuretic use.
- Patients with high urine chloride (>15 mEq/L [15 mmol/L]), hypertension, and hypokalemia who do not appear to be overtly volume overloaded should be evaluated for a mineralocorticoid excess disorder (saline-resistant metabolic alkalosis) such as Cushing syndrome and primary hyperaldosteronism.

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Item 67 Answer: A

Educational Objective: Manage end-stage kidney disease with dialysis.

The most appropriate management is to initiate dialysis (**Option A**). The history and physical examination findings suggest that this patient has had long-standing uncontrolled hypertension. The small (<9 cm) echogenic kidneys seen on kidney ultrasound indicate that he has had advanced chronic kidney disease (CKD), likely for years. When patients present with "acute" kidney injury, a late presentation of end-stage kidney disease (ESKD) must be part of the differential diagnosis. History, physical examination, and laboratory indices may not be able to distinguish between acute and chronic disease. However, the ultrasound finding of small echogenic kidneys is very consistent with advanced CKD. Initiation of dialysis for symptoms of uremia and severe metabolic acidosis is the most appropriate next step for this patient, regardless of the cause or duration of his kidney disease.

A rapid volume challenge through intravenous 0.9% saline (**Option B**) is most appropriate for patients with acute prerenal kidney injury, but it may provoke heart failure in this patient with ESKD.

Intravenous high-dose glucocorticoids such as methylprednisolone (**Option C**) are initiated for patients with acute glomerulonephritis with rapid decline in kidney function; this therapy would not be efficacious in patients, such as this one, with advanced CKD.

A percutaneous kidney biopsy (**Option D**) is indicated only if a reversible or treatable cause of kidney disease is suspected, but it is not helpful or practical in patients with small echogenic kidneys that indicate irreversible kidney disease. Finally, percutaneous kidney biopsy is relatively contraindicated in patients with small kidneys because of increased risk for bleeding.

KEY POINTS

- When patients present with presumed acute kidney injury, a late presentation of end-stage kidney disease must be part of the differential diagnosis.
- History, physical examination, and laboratory indices often do not discriminate between acute and chronic kidney disease (CKD); however, small (<10 cm) echogenic kidneys on ultrasound is very consistent with advanced CKD.

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Item 68 Answer: B

Educational Objective: Adjust an antihypertensive medication regimen using combination drug therapy.

The most appropriate additional treatment is amlodipine, a calcium channel blocker (CCB) (**Option B**). This patient with hypertension requires escalation of her antihypertensive medication regimen because her blood pressure (BP) is not at target. The 2017 American College of Cardiology/American Heart Association BP guideline recommends a BP target of <130/80 mm Hg. Two strategies can be used: maximize medication dose before adding another agent or add another agent from a different class of medication before maximizing the dose of the prior agents. There are no randomized trials

comparing these strategies. Generally, there is diminishing return in BP lowering if dose is titrated up from 50% to 100% of maximum. Also, it is unlikely that increasing the dose of a drug from 50% to 100% of maximum will result in a significant BP reduction. Finally, titration to maximum doses more commonly results in side effects and may reduce medication adherence. Therefore, adding a third drug to a two-drug regimen is a strategy recommended by many experts.

Two drugs from classes that target the same BP control system are less effective and potentially harmful when used together. For example, administration of combination therapy with renin-angiotensin system blockers, such as an ACE inhibitor with an angiotensin receptor blocker (ARB) or an ACE inhibitor or ARB with the direct renin inhibitor aliskiren, increases cardiovascular and renal risk. Therefore, aliskiren should not be added (**Option A**).

Hydralazine (**Option C**) is not the best option, because agents shown to reduce clinical events (such as thiazide diuretics, calcium channel blockers, ACE inhibitors, ARBs) should be used preferentially. Additionally, it is a thrice-daily medication. Use of longer-acting antihypertensive drugs that only require once-daily dosing and combination pills to reduce pill burden can increase adherence.

Adding hydrochlorothiazide (**Option D**) is not the best option because two thiazide diuretics will not improve BP control in this patient and risks the development of hypokalemia. However, concomitant use of diuretics that have different mechanisms of action, such as a combination of a thiazide diuretic, potassium-sparing diuretic, and/or a loop diuretic, can effectively control extracellular volume and hypertension.

KEY POINTS

- Two strategies can be used for antihypertensive dose adjustment in the treatment of hypertension: maximize medication dose before adding another agent or add another agent before maximizing the dose of the prior agents.
- Two drugs from classes that target the same blood pressure control system are less effective and potentially harmful when used together.

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Item 69 Answer: B

Educational Objective: Diagnose nephrolithiasis during pregnancy.

The most appropriate diagnostic test to perform next is kidney ultrasonography (**Option B**) for this pregnant patient with likely nephrolithiasis. Imaging is indicated for diagnosis and to guide management based on stone size and location. Ultrasonography is increasingly being used as an initial diagnostic study. Although less sensitive than CT for nephrolithiasis, particularly for detecting small stones and ureteral stones, ultrasonography does not expose patients to radiation and is typically more readily available and has a lower cost compared with CT; it is also the preferred modality during pregnancy. A positive ultrasound may therefore be adequate for initial diagnosis in patients with a typical presentation for kidney stones; more complex testing is indicated for those with a high clinical suspicion but a nondiagnostic ultrasound or a more complicated clinical presentation.

Abdominal MRI (**Option A**) can be used during pregnancy, but it is not optimal for imaging kidney stones. Ultrasonography is preferred, although MRI may be a diagnostic option if additional imaging is required for diagnosis.

Plain abdominal radiography (**Option C**) has limited utility due to its inability to detect radiolucent uric acid stones, and it does not provide as much anatomic information as other modalities; furthermore, it should be avoided during pregnancy. However, it may be useful in assessing stone burden in nonpregnant patients with known radiopaque stones.

Noncontrast helical abdominal CT (**Option D**) has traditionally been the most commonly used imaging technique because it detects most stones, provides anatomic information, and visualizes the entire urinary tract; it may also suggest stone composition and potentially provide alternative diagnoses if nephrolithiasis is not detected. Although CT is more sensitive and specific than ultrasonography, a randomized controlled trial demonstrated equivalent diagnostic accuracy within the emergency department. Finally, CT is associated with significant radiation exposure and is contraindicated in pregnant women.

Ureteroscopy (**Option E**), in which an endoscopic device is introduced in a retrograde fashion into the ureter through the bladder, is most commonly used in the management of mid-ureteral and distal ureteral stones, using a combination of catheter-based stone disintegration methods (such as laser lithotripsy), stone baskets, and ureteral stent placement. Although this procedure does not involve radiation, it is not a diagnostic procedure indicated for suspected kidney stones because it is unnecessarily invasive.

KEY POINTS

- Ultrasonography is readily available, inexpensive, and very safe and is a useful first study in evaluating nephrolithiasis.
- Kidney ultrasonography is the preferred diagnostic test for suspected nephrolithiasis in pregnant women.

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Item 70 Answer: C

Educational Objective: Treat acute kidney injury due to tumor lysis syndrome.

The most appropriate additional treatment is rasburicase (**Option C**). This young patient exhibits spontaneous tumor

H CONT. lysis syndrome (TLS) before the initiation of chemotherapy. TLS is characterized by acute kidney injury with severe hyperuricemia, hyperphosphatemia, and hypocalcemia. These electrolyte abnormalities can lead to cardiac arrhythmias, seizures, and death. TLS is most frequently seen in highly proliferative hematologic malignancies such as acute leukemia and high-grade lymphomas but can develop in many other cancers. Appropriate therapy includes prompt initiation of isotonic volume expansion and an agent such as rasburicase. Rasburicase is a urate oxidase enzyme that metabolizes urate to allantoin, a significantly more water-soluble compound.

Allopurinol (**Option A**) is the most commonly used urate-lowering agent. It competitively inhibits the enzyme xanthine oxidase, blocking the conversion of hypoxanthine (a breakdown product of purines) to urate. Although allopurinol will prevent new urate formation, it will not rapidly lower this patient's existing serum urate level.

Febuxostat (**Option B**) is a noncompetitive xanthine oxidase inhibitor and, as with allopurinol, blocks the formation of urate. Febuxostat is often used in patients in whom allopurinol is contraindicated. However, it is less effective than rasburicase in rapidly lowering serum urate levels.

The role of urinary alkalinization in TLS (**Option D**) with either acetazolamide and/or sodium bicarbonate is unclear and controversial. Alkalinization was recommended to increase promote uric acid solubility. However, alkalinization of the urine can also promote a favorable environment for precipitation of calcium phosphate. Therefore, isotonic saline and rasburicase are preferred to prevent or treat TLS.

KEY POINTS

- Tumor lysis syndrome may spontaneously occur in patients with acute leukemia or high-grade lymphoma and is characterized by acute kidney injury with severe hyperuricemia, hyperphosphatemia, and hypocalcemia.
- Treatment of tumor lysis syndrome includes prompt initiation of isotonic volume expansion and rasburicase to rapidly reduce serum urate levels.

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Item 71 Answer: D

Educational Objective: Diagnose nephrolithiasis with noncontrast helical CT.

The most sensitive imaging test to perform is a noncontrast helical abdomen and pelvis CT (**Option D**), which has the highest sensitivity and specificity of all imaging options used in evaluating nephrolithiasis. The sensitivity of noncontrast helical abdominal CT for the diagnosis of nephrolithiasis is greater than 95%. Noncontrast helical CT can also detect stones independent of their composition, with the exception of stones composed of indinavir crystals. Furthermore, noncontrast helical CT may be able to predict the composition of the stone based on the Hounsfield units. However, this should not preempt stone analysis. Finally, noncontrast helical CT potentially provides alternative diagnoses if nephrolithiasis is not detected.

There is no role for the use of intravenous pyelography (IVP) (**Option A**) in the evaluation of kidney stones. IVP has high sensitivity for the diagnosis of hydronephrosis that might be caused by a stone but lacks the sensitivity and specificity of noncontrast helical CT in the diagnosis of nephrolithiasis and potential diagnosis of stone type. When noncontrast helical CT is unavailable or contraindicated, kidney ultrasonography is preferred to IVP. Finally, IVP requires the use of intravenous contrast.

Kidney and bladder ultrasonography (**Option B**) is less accurate than noncontrast helical CT in the diagnosis of nephrolithiasis. Sensitivity ranges from 50% to 90%. Small stones and stones within the ureter are frequently not detected on ultrasonography. Ultrasonography is also less able to determine stone size or location within the ureter. However, if noncontrast CT is unavailable or if the patient is pregnant, ultrasonography is the preferred method of evaluation.

Radiography (**Option C**) has little role in the evaluation of kidney stones due to poor sensitivity and specificity. This modality will not detect radiolucent uric acid stones and often cannot determine if the calcification visualized is within or external to the urinary system. Because of low cost and low amount of radiation, radiography is useful for following the movement and growth of a stone as well as monitoring total stone burden.

KEY POINTS

- Noncontrast helical CT of the abdomen and pelvis is the gold standard for diagnosis of kidney stones because of its high sensitivity and specificity.
- Ultrasonography is the preferred imaging test for suspected nephrolithiasis in pregnant women and when CT imaging is not available.

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Item 72 Answer: D

Educational Objective: Treat metabolic acidosis in chronic kidney disease.

The most appropriate treatment is sodium bicarbonate supplement (**Option D**) for this patient with a metabolic acidosis. There is a strong association between metabolic acidosis and increased progression of chronic kidney disease (CKD) and mortality. Data suggest that repletion of bicarbonate attenuates the rate of CKD progression. Bicarbonate can be given as sodium bicarbonate tablets, as a powder (including in the form of baking soda), or through a diet rich in fruit and vegetables that are endogenous

alkali sources. Guidelines recommend initiation of bicarbonate when the serum bicarbonate level is <22 mEq/L (22 mmol/L), as seen in this patient. Bicarbonate therapy should be titrated to achieve a serum bicarbonate level within the normal range.

FDA black box warnings for use of erythropoietin-stimulating agents (ESAs) (**Option A**) include the risk for increased mortality and/or tumor progression in patients with active malignancy; increased risk for thromboembolic events in postsurgical patients not receiving anticoagulant therapy; and increased risk for serious cardiovascular events when ESAs are administered to patients with hemoglobin values >11 g/dL (110 g/L) or with a history of stroke. Because of the potential harm caused by ESAs in patients with CKD, use of these agents should be restricted to patients with hemoglobin values <10 g/dL (100 g/L) and symptoms.

Hemodialysis (**Option B**) is not an appropriate management, as this patient has stage G4 CKD. Medical management of metabolic acidosis is indicated for these patients until progression to advanced stage G5 CKD with an estimated glomerular filtration rate <10 mL/min/1.73 m^2. For patients with advanced stage G5 CKD, data indicate that there is no mortality benefit to early initiation of renal replacement therapy. The decision to start hemodialysis should be based upon the development of uremic symptoms refractory to medical management.

A high-protein diet (**Option C**) is a source of the daily acid load and would worsen rather than improve this patient's metabolic acidosis.

KEY POINTS

- Metabolic acidosis in patients with chronic kidney disease should be treated with alkali therapy when serum bicarbonate levels are <22 mEq/L (22 mmol/L).
- Repletion of bicarbonate into the normal range in patients with chronic kidney disease (CKD) attenuates the rate of CKD progression.

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Item 73 Answer: D

Educational Objective: Diagnose thin glomerular basement membrane disease.

Thin glomerular basement membrane (GBM) disease (**Option D**) is the most likely diagnosis. Also known as benign familial hematuria, inheritance in this disease is autosomal dominant. The inherited type IV collagen abnormality causes thinning of the GBM, which results in hematuria but usually without proteinuria or abnormal kidney function. Thin GBM disease may affect up to 5% of the population, with up to 50% of patients who are diagnosed reporting a family history of hematuria without kidney failure. Both microscopic and macroscopic hematuria can be seen, first manifesting in young adulthood. Although diagnosis can be made by kidney biopsy, this is not usually required in the setting of a good clinical and family history. Genetic testing may also be used to make the diagnosis.

Autosomal dominant tubulointerstitial kidney disease (**Option A**) should be suspected in patients with slowly progressive chronic kidney disease, a bland urine sediment, small kidneys, and a family history of end-stage kidney disease. This patient has normal-sized kidneys, microscopic hematuria, and no family history of kidney dysfunction.

Fabry disease (**Option B**) follows an X-linked pattern on inheritance. Patients are expected to have kidney dysfunction by adulthood alongside abnormalities in other organs such as the skin (telangiectasias and angiokeratomas), eyes, heart (premature coronary artery disease), brain, and/or peripheral nervous system (severe neuropathic pain). This patient has no kidney dysfunction or other organ abnormalities.

Hereditary nephritis (Alport syndrome) (**Option C**) follows an X-linked pattern on inheritance in 85% of cases; the remaining 15% of cases follow an autosomal recessive pattern of inheritance. In addition, hereditary nephritis is expected to have a family history of not only hematuria, but also proteinuria (unlike this patient), renal dysfunction (including end-stage kidney disease in most families), and both visual and hearing abnormalities.

KEY POINT

- Thin glomerular basement membrane (GBM) disease is an autosomal dominant type IV collagen abnormality that causes thinning of the GBM, resulting in hematuria but usually without proteinuria or abnormal kidney function.

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Item 74 Answer: A

Educational Objective: Treat hypertension in an older patient with cardiovascular disease.

The most appropriate management is to add chlorthalidone (**Option A**). Guidelines differ in recommendations for systolic blood pressure (SBP) goals in older patients. The American College of Cardiology/American Heart Association recommend an SBP of <130 mm Hg in noninstitutionalized, ambulatory community-dwelling adults ≥65 years of age, whereas the American College of Physicians (ACP)/American Academy of Family Physicians (AAFP) recommend an SBP of <150 mm Hg in most patients >60 years of age to minimize treatment-related harms. However, ACP/AAFP also recommend considering initiating or intensifying treatment in some adults >60 years of age at high cardiovascular risk to an SBP <140 mm Hg to reduce the risk for stroke or cardiac events. Because this

patient with diabetes mellitus, peripheral vascular disease, and hyperlipidemia is at high risk for stroke or cardiac events, initiation of a second first-line antihypertensive drug such as chlorthalidone or a calcium channel blocker is reasonable.

The initiation of antihypertensive drug therapy with a single agent followed by the addition of other agents is reasonable in the very elderly or those at risk for drug interactions or side effects. Guidelines recommend that the second drug should work by a different mechanism and include a typical first-line agent such as a calcium channel blocker, thiazide diuretic, ACE inhibitor, or angiotensin receptor blocker (ARB); however, ACE inhibitor/ARB combinations are not recommended. α-Blockers such as prazosin (**Option B**) are not used as first-line therapy for hypertension because they are less effective for prevention of cardiovascular disease than other first-line agents such as thiazide diuretics.

Adults with hypertension and peripheral artery disease (PAD) should be treated similarly to patients with hypertension without PAD. There is also no evidence that any one class of antihypertensive medication or strategy is superior. Therefore, there is no indication to switch this patient from lisinopril to ramipril (**Option C**).

Continuing current medical therapy (**Option D**) may place this older patient at increased risk for cardiovascular events. Although guideline targets for SBP differ, the benefit of SBP reduction to <130-140 mm Hg in older patients at increased risk for stroke or cardiovascular events is likely to exceed harms.

KEY POINT

- Although guidelines differ in recommendations for systolic blood pressure (SBP) targets, the benefit of SBP reduction to <130-140 mm Hg in older patients at increased risk for stroke or cardiovascular events is likely to exceed harms.

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Item 75 Answer: C

Educational Objective: Diagnose membranous nephropathy using noninvasive testing.

Anti-phospholipase A2 receptor (PLA2R) antibody (**Option C**) testing is the most appropriate diagnostic test to perform next. This patient with the nephrotic syndrome and venous thromboembolism most likely has membranous nephropathy. Patients with membranous nephropathy are particularly prone to thrombotic complications. These clots include lower extremity, pulmonary, and renal vein thromboses; they can occur in up to 25% of patients and are most likely to occur within the first 6 months of diagnosis. The risk for clotting increases when serum albumin is <2.8 g/dL (28 g/L) and increases proportionally with decreasing serum albumin levels. The diagnosis of primary membranous nephropathy can be made noninvasively using serum anti-PLA2R antibody testing. Anti-PLA2R antibodies are nearly 100% specific for primary membranous nephropathy and can obviate the need for kidney biopsy in patients with preserved kidney function and no evidence of secondary causes as well as in patients with a clear contraindication to kidney biopsy.

ANCA-associated vasculitis typically presents as a rapidly progressive glomerulonephritis characterized by a rapid decline in kidney function and erythrocytes and erythrocyte casts on urine microscopy. These findings are not present in this patient; therefore, ANCA antibody testing (**Option A**) is not appropriate.

Anti–double-stranded DNA antibodies (**Option B**) are highly specific in establishing the diagnosis of systemic lupus erythematosus. Although class V lupus nephritis is a cause of secondary membranous nephropathy, normal complement levels and negative antinuclear antibody testing rule out lupus nephritis.

Stopping anticoagulation to perform a kidney biopsy (**Option D**) in this patient with venous thromboembolism is high risk; therefore, the next step in management should be anti-PLA2R testing, which, if positive, is a definitive diagnosis of membranous nephropathy.

KEY POINTS

- Serologic testing for anti-phospholipase A2 receptor antibodies is a noninvasive test that approaches 100% specificity for primary membranous nephropathy.
- Serologic testing for anti-phospholipase A2 receptor antibodies can eliminate the need for kidney biopsy in patients with preserved kidney function and no evidence of secondary causes as well as in patients with a clear contraindication to kidney biopsy.

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Item 76 Answer: A

Educational Objective: Recognize chronic kidney disease as an independent risk factor for cardiovascular disease.

The most likely expected cause of premature death in this patient is cardiovascular disease (**Option A**). Patients with stage G3 chronic kidney disease (CKD) are more likely to die of a cardiovascular event than they are to progress to stage G4 CKD or to end-stage kidney disease (ESKD) that requires initiation of renal replacement therapy. Also, the risk for cardiovascular-related death in patients with stages G3 and G4 CKD is four to five times higher than the risk for progression to ESKD (**Option B**). CKD and albuminuria are both independent risk factors for cardiovascular disease. Mortality risk in these patients increases with a decreasing estimated glomerular filtration rate and increasing albuminuria. Therefore, management of CKD addresses traditional cardiovascular risk factors, such as blood pressure control, glycemic control for

patients with diabetes mellitus, and treatment of hyperlipidemia.

Infection is the second leading cause of death in ESKD (**Option C**). Patients are at increased risk due to a relatively immunosuppressed state from chronic inflammation and frequent exposure to the health care environment, including long-term need for vascular access and related-risk of bacteremia and sepsis. Infecting organisms are usually common organisms such *as Staphylococcus aureus* acquired through hemodialysis.

Acquired cystic kidney disease becomes more common and progresses during the course of ESKD, and some studies suggest that it may affect >50% of patients who have had ESKD for >3 years. The epithelial cells lining these cysts may undergo malignant transformation by poorly understood mechanisms. Patients with ESKD have a markedly increased risk for renal cell carcinoma (**Option D**); however, malignancy is only the third leading cause of death in patients with ESKD, and renal cell carcinoma comprises only a portion of malignancy-related deaths. Routine screening is not recommended, but a high level of suspicion is warranted in patients with symptoms such as new-onset gross hematuria or unexplained flank pain.

KEY POINT

- Cardiovascular disease is the leading cause of death among patients with chronic kidney disease, and management should address cardiovascular risk factors, such as blood pressure control, glycemic control, and treatment of hyperlipidemia.

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Item 77 Answer: B

Educational Objective: Diagnose heme pigment nephropathy.

The most likely diagnosis is heme pigment nephropathy (**Option B**). This patient likely has underlying glucose-6-phosphate dehydrogenase (G6PD) deficiency, and acute hemolytic anemia due to primaquine exposure. Primaquine can precipitate hemolytic anemia in such patients, as can other antimalarial agents, rasburicase, sulfonamides (e.g., sulfamethoxazole), some nonsulfa antibiotics (e.g., isoniazid), dapsone, and nitrofurantoin. Myoglobin and hemoglobin are heme pigment–containing proteins that can cause acute kidney injury (AKI). Heme pigment nephropathy occurs when large amounts of heme pigment are released into the circulation due to massive intravascular hemolysis. Pigment nephropathy can cause acute tubular necrosis as the result of volume depletion, renal vasoconstriction, direct heme protein–mediated cytotoxicity, and intraluminal cast formation. Laboratory findings include anemia, increased serum lactate dehydrogenase, decreased haptoglobin, and increased serum creatinine. The urine dipstick is positive for blood in the absence of erythrocytes. Other urinary findings include pigmented granular casts and hemoglobinuria. Both myoglobinuria and hemoglobinuria can cause tea-colored urine and urine dipstick positive for blood; however, hemoglobin produces a reddish-brown color in centrifuged serum and myoglobin does not discolor the serum. The treatment is expansion of the intravascular volume with 0.9% saline.

Although primaquine is a newly initiated medication, the short time course and absence of pyuria are not consistent with drug-induced acute interstitial nephritis (**Option A**).

In this patient, the presence of a urine dipstick positive for blood in the absence of erythrocytes and numerous pigmented granular casts supports the diagnosis of heme pigment nephropathy rather than prerenal AKI (**Option C**), which is associated with a benign urinalysis.

When exposed to an oxidative stress, patients with G6PD deficiency can develop acute hemolytic anemia. Rhabdomyolysis (**Option D**) is not part of the clinical syndrome. However, the clinical course of rhabdomyolysis is similar to that of pigment nephropathy due to hemolysis. Laboratory findings of rhabdomyolysis-induced AKI include hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, metabolic acidosis, elevated serum creatinine, and elevated muscle enzymes such as serum creatine kinase (typically >5000 U/L), lactate dehydrogenase, and aspartate and alanine aminotransferases.

KEY POINTS

- Myoglobin and hemoglobin are heme pigment–containing proteins that can cause acute kidney injury.
- Heme pigment nephropathy is associated with a positive urine dipstick for blood in the absence of erythrocytes and the presence of pigmented granular casts.

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Item 78 Answer: A

Educational Objective: Identify ferric carboxymaltose as the cause of hypophosphatemia.

The most likely cause of this patient's hypophosphatemia is ferric carboxymaltose (**Option A**). This parenteral iron solution can be administered in a single dose and thus has been increasingly used to treat individuals with severe iron deficiency that cannot be corrected with oral preparations. However, this medication can result in transient hypophosphatemia. Although most reported cases occur after a patient receives repeated doses, hypophosphatemia has occurred after a single dose. The decrease in serum phosphorus is typically not significant, but for patients with risk factors (e.g., vitamin D deficiency, malnutrition, gastrointestinal

disease, or use of medications that bind phosphorus in the gut), severe symptomatic hypophosphatemia has occurred. The mechanism has shown to be secondary to increases in fibroblast growth factor 23 (FGF-23), which cause phosphaturia and a decrease in 1-hydroxylation of vitamin D. Other causes of hypophosphatemia include hungry bone syndrome following parathyroidectomy; refeeding of starved individuals; oncogenic osteomalacia associated with sarcomas that secrete FGF-23; and X-linked hypophosphatemic rickets due to a mutation that causes increased FGF-23. It can also occur following liver resection in a living liver donor.

A low phosphorus diet (**Option B**) is not the cause of this patient's hypophosphatemia. The kidney can reduce phosphorus excretion to very low levels, but only a severely phosphate-restricted diet will decrease the serum phosphorus levels (significantly more frequently in women). In addition, the high fractional excretion of phosphorus identifies renal wasting of phosphorus and excludes poor dietary intake as the cause of her hypophosphatemia.

This patient's serum bicarbonate level is low, suggesting either metabolic acidosis (**Option C**) or compensation for respiratory alkalosis. Because there is no evidence of an increased respiratory rate, the low serum bicarbonate level most likely represents a metabolic acidosis. Although metabolic acidosis and respiratory alkalosis can shift phosphorus into cells, metabolic acidosis has a minimal effect and thus would not be the cause of this patient's hypophosphatemia. Additionally, the elevated fractional excretion of phosphorus eliminates intracellular shift of phosphorus as the cause of her hypophosphatemia.

Although prednisone (**Option D**) can cause muscle breakdown and interfere with vitamin D metabolism, it does not typically cause hypophosphatemia.

KEY POINT

- Ferric carboxymaltose, an intravenous iron preparation, has been associated with hypophosphatemia by causing renal phosphate wasting.

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Item 79 Answer: B

Educational Objective: Treat primary hyperaldosteronism.

Initiating eplerenone therapy (**Option B**) is the most appropriate next step in management. This patient with resistant hypertension was evaluated for secondary causes of hypertension. A plasma aldosterone concentration/plasma renin activity ratio >20 with a plasma aldosterone concentration of at least 15 ng/dL (414 pmol/L) is considered a positive result for primary aldosteronism and patients should be referred to an endocrinologist or nephrologist, who may perform additional testing to confirm inappropriate aldosterone secretion in a salt-replete state. Primary hyperaldosteronism is the most common cause of secondary hypertension in middle-aged adults and an important cause of resistant hypertension. In this patient, a dedicated adrenal CT scan shows diffuse bilateral adrenal hyperplasia, as seen in two thirds of patients with primary hyperaldosteronism. Diffuse bilateral hyperplasia is managed by an aldosterone receptor antagonist such as eplerenone.

Bilateral adrenal vein sampling (**Option A**) for aldosterone is used to distinguish between unilateral adenoma and bilateral hyperplasia in patients who are surgical candidates and would like to pursue surgical management. Functioning adrenal adenomas can be very small and may not be detected with advanced imaging, but they can be implicated as a cause of primary hyperaldosteronism if aldosterone secretion lateralizes to one gland. This patient has multiple comorbid conditions and does not want to pursue any surgical procedures. Therefore, adrenal vein sampling is not indicated.

An MRI of the adrenal glands (**Option C**) is not indicated because CT of the adrenal glands, which was already performed, has superior spatial resolution compared with MRI for the assessment of adrenal glands.

In most patients, the diagnosis of primary hyperaldosteronism is confirmed by additional testing following a positive screening test. The oral sodium loading test is performed to detect autonomous aldosterone secretion following sodium chloride loading, either orally or by intravenous infusion. However, this confirmatory test is only performed after the patient's blood pressure is controlled and hypokalemia corrected. Although oral sodium loading (**Option D**) is a possible confirmatory test, it should not be initiated in this patient at this time.

KEY POINTS

- Primary hyperaldosteronism is the most common cause of secondary hypertension in middle-aged adults and an important cause of resistant hypertension.
- Primary hyperaldosteronism is most commonly caused by bilateral adrenal hyperplasia and is managed by an aldosterone receptor antagonist.

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Item 80 Answer: B

Educational Objective: Diagnose a mixed acid-base disorder.

The most likely acid-base disorder is a respiratory alkalosis and normal gap metabolic acidosis (**Option B**). The first step in the interpretation of acid-base disorders usually requires the identification of the likely dominant or primary acid-base disorder, followed by an assessment of the compensatory response. When measured values fall outside the expected compensatory range, a mixed acid-base disorder is considered

H CONT. present. The primary disorder is usually reflected by the blood pH. Appropriate compensation may result in near-normal pH but never a normal pH. In patients with an obvious acid-base disturbance (for example, an abnormal serum bicarbonate), a normal pH suggests the presence of a mixed acid-base disorder. In this case, the patient's pH of 7.4 does not allow for a clear assignment of the primary disorder and therefore indicates a mixed acid-base disorder. The patient has a P_{CO_2} of 27 mm Hg (3.6 kPa), suggesting the presence of a respiratory alkalosis. The expected metabolic compensation for chronic respiratory alkalosis is a reduction in the serum bicarbonate of 4 to 5 mEq/L (4-5 mmol/L) for each 10 mm Hg (1.3 kPa) decrease in the P_{CO_2}. In this case, the decrease in P_{CO_2} is 13 mm Hg (1.7 kPa); thus, the serum bicarbonate is expected to be 5.2 to 6.5 mEq/L (5.2-6.5 mmol/L) lower than normal. Therefore, expected serum bicarbonate would be calculated as follows:

Normal Bicarbonate - Expected Compensation
24 - (5.2-6.5) mEq/L (mmol/L) = 17.5-18.8 mEq/L (17.5-18.8 mmol/L)

The patient's serum bicarbonate of 16 mEq/L (16 mmol/L) is lower than expected, indicating the presence of a concurrent metabolic acidosis. The anion gap of 7 is normal, indicating a normal anion gap metabolic acidosis.

Respiratory alkalosis with an increased anion gap metabolic acidosis (**Option A**) is not correct because the anion gap is 7, and thus not exceeding the normal threshold of 8.0 to 10 mEq/L ± 2.0 mEq/L (8.0-10 mmol/L ± 2.0 mmol/L).

Respiratory alkalosis, normal anion gap metabolic acidosis, and metabolic alkalosis (**Option C**) is not correct because the serum bicarbonate is lower, not higher, than the expected compensatory response.

Respiratory alkalosis with chronic compensation (**Option D**) is partially correct but does not account for the serum bicarbonate level being lower than the expected compensatory response, which indicates a concurrent metabolic acidosis.

KEY POINTS

- The first step in the interpretation of acid-base disorders requires the identification of the likely dominant acid-base disorder, followed by an assessment of the compensatory response.
- In the interpretation of acid-base disorders, when measured values fall outside the expected compensatory range, a mixed acid-base disorder is present.

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Item 81 Answer: D

Educational Objective: Diagnose hepatitis C virus infection as the cause of cryoglobulinemic glomerulonephritis.

The most appropriate viral study to perform is hepatitis C virus (HCV) antibody testing (**Option D**), and if positive, viral load measurement and genotyping. This patient's clinical presentation (purpuric rash) and laboratory results (low complement levels, positive rheumatoid factor, and positive cryoglobulins) support the diagnosis of cryoglobulinemic glomerulonephritis; biopsy is most likely to reveal membranoproliferative glomerulonephritis (MPGN). Cryoglobulinemia denotes the presence of clonal or polyclonal immunoglobulins that precipitate in the serum at temperatures <37.0 °C (98.6 °F) and dissolve with rewarming. Cryoglobulinemia is classified as type I, II, or III based on the composition of the cryoglobulins. Type I cryoglobulinemia involves a monoclonal immunoglobulin, usually IgM, and is associated with plasma cell dyscrasias. Types II and III are called mixed cryoglobulinemia; they are composed of a mixture of polyclonal IgG and monoclonal or polyclonal IgM. Mixed cryoglobulinemia is usually seen in association with infections such as HCV, connective disorders, and, rarely, lymphoproliferative disorders. Cutaneous symptoms (palpable purpura, Raynaud phenomenon, ulcers, necrosis, and livedo reticularis) predominate in 70% to 90% of patients with mixed cryoglobulinemia. Peripheral neuropathy (60%), arthritis (40%), and glomerulonephritis (40%) are common. An estimated 2% to 3% of the world population has HCV, but higher prevalence rates are seen in certain geographic locations, such as Egypt, where >10% of the population has HCV. Treatment of cryoglobulinemic glomerulonephritis due to HCV infection is aimed at eradication of the virus using direct-acting antiviral drugs with or without concomitant immunosuppression based on severity of disease.

Hepatitis A virus (**Option B**) infection has not been associated with specific glomerular lesions. Although hepatitis B virus (HBV) infection and HIV infection (**Options A, C**) have been linked to glomerular diseases, these have classically been nephrotic syndromes, specifically membranous nephropathy with HBV and focal segmental glomerulosclerosis with HIV. This patient has a nephritic syndrome not compatible with HBV- or HIV-associated glomerular diseases.

KEY POINTS

- Hepatitis C virus infection is associated with cryoglobulinemic glomerulonephritis.
- Treatment of hepatitis C–associated cryoglobulinemic glomerulonephritis is direct-acting antiviral drugs.

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Item 82 Answer: B

Educational Objective: Treat hypertension in a patient with chronic kidney disease and an estimated glomerular filtration rate <30 mL/min/1.73 m².

The most appropriate treatment for this patient is to discontinue hydrochlorothiazide and begin furosemide (**Option B**).

Because sodium retention and volume overload are major contributory factors in the hypertension of chronic kidney disease (CKD), dietary sodium restriction to <2000 mg/d and addition of a diuretic are both essential for control of blood pressure (BP), especially in advanced CKD. Higher doses of diuretics are required in patients with CKD due to decreased glomerular filtration rate (GFR). Hydrochlorothiazide is not an effective diuretic in this patient who has advanced CKD with an estimated GFR (eGFR) <20 to 30 mL/min/1.73 m^2, as evidenced by his elevated BP, lower extremity edema, and hyperkalemia after 1 month of treatment. Loop diuretics, dosed two or three times daily, are more potent diuretics and preferred in patients who have advanced CKD with an eGFR <20 to 30 mL/min/1.73 m^2.

Eplerenone (**Option A**) is not appropriate treatment for this patient because of several factors. The addition of an aldosterone receptor blocker such as eplerenone to an ACE inhibitor such as lisinopril will result in dual renin-angiotensin system inhibition and will further increase the serum potassium level. Additionally, potassium-sparing diuretics, such as aldosterone receptor blockers (spironolactone or eplerenone) or epithelial sodium channel blockers (amiloride), are weaker diuretics. Although aldosterone receptor blockers are recommended for certain patients with resistant hypertension, they are not first-line diuretic agents for BP management in patients with CKD and eGFR <20 to 30 mL/min /1.73 m^2.

Increasing this patient's dose of hydrochlorothiazide (**Option C**) will not reduce this patient's BP or edema. Thiazide diuretics such as hydrochlorothiazide become increasingly ineffective as GFR decreases.

According the American College of Cardiology/American Heart Association, adults with hypertension and CKD should be treated to a BP goal of <130/80 mm Hg. Continuing the current management (**Option D**) is inappropriate, as the patient has not achieved the desired BP target, and has edema and hyperkalemia.

KEY POINTS

- Sodium retention and volume overload are major contributory factors in the hypertension of chronic kidney disease.
- Loop diuretics, dosed two or three times daily, are preferred to thiazide diuretics in patients with hypertension and an estimated glomerular filtration rate <20 to 30 mL/min/1.73 m^2.

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Item 83 Answer: E

Educational Objective: Evaluate the cause of proteinuria.

The most appropriate test to perform next is a urine protein electrophoresis (**Option E**). This patient has an unexplained elevation of serum creatinine, indicating the presence of kidney disease. Assessment for urine protein is indicated in patients with any suspected kidney disease. Albumin is the predominant protein detected on urine dipstick. However, although proteinuria is most commonly comprised of albumin, other proteins, including kidney-derived low-molecular-weight proteins, monoclonal immunoglobulins and light chains, myoglobin, and hemoglobin, may be present. In this case, there was a discrepancy between the semiquantification of urine protein by dipstick and the urine protein-creatinine ratio, which raises concern for the excretion of protein other than albumin. In addition, the patient also has a normocytic, normochromic anemia. The combination of these findings strongly suggests the possibility of multiple myeloma. A urine electrophoresis and urine examination for light chains should be performed to help establish the diagnosis.

A repeat urinalysis (**Option A**) will not clarify the discrepancy between the urine dipstick and urine protein-creatinine ratio. The urine protein-creatinine ratio has identified significant proteinuria, which now must be investigated.

Quantification of proteinuria has traditionally been performed with a 24-hour urine collection (**Option B**), which measures all proteins present in the urine. Due to challenges in feasibility, accuracy, and patient adherence, measurement of proteinuria is now typically performed by determining the ratio of protein or albumin to creatinine on random urine samples. These ratios are easily obtained and correlate well with timed collections.

The sulfosalicylic acid test (**Option C**) can be used to detect the presence of not only albumin but also other proteins that are not detected with the urine dipstick, such as urine light chains or immunoglobulins. However, this test will simply confirm that the urine contains nonalbumin proteins, which has already been determined by the urine protein-creatinine ratio, but will not specifically identify light chains or immunoglobulins.

The urine albumin-creatinine ratio (**Option D**) measures only albumin in the urine. Although this test is helpful in evaluating for diabetic kidney disease, it will not determine the nature of the nonalbumin protein found in this patient's urine.

KEY POINTS

- The presence of significant measured proteinuria via urine protein-creatinine ratio in the context of minimal proteinuria on urine dipstick suggests the presence nonalbumin proteinuria.
- Nonalbumin proteinuria may include kidney-derived low-molecular-weight proteins, monoclonal immunoglobulins and light chains, myoglobin, and hemoglobin.

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Item 84 Answer: C

Educational Objective: Diagnose rhabdomyolysis as a cause of hyperphosphatemia.

The most likely cause of this patient's hyperphosphatemia is atorvastatin-induced rhabdomyolysis (**Option C**) and is evidenced by the patient's elevated serum creatine kinase level. The cause of hyperphosphatemia can often be determined from the clinical history and is most commonly due to chronic kidney disease (CKD) or acute kidney injury. Because phosphate is primarily an intracellular anion, widespread cellular damage as occurs in rhabdomyolysis and tumor lysis syndrome increases serum phosphate, especially if the glomerular filtration rate (GFR) is decreased. Hyperphosphatemia can also be associated with diabetic ketoacidosis and, less commonly, lactic acidosis. Excessive phosphate intake rarely causes hyperphosphatemia because the kidney rapidly excretes phosphate. However, phosphate-containing cathartics can cause acute elevations in serum phosphate, especially in patients with reduced GFR. The risk for statin-induced serious muscle injury, including rhabdomyolysis, is <0.1%. Discontinuation of the statin in a patient with statin-induced myopathy is typically followed by a decreasing creatine kinase and resolution of symptoms, but recovery can be prolonged in patients with more severe muscle injury.

Although hyperphosphatemia is common in stage G4 or G5 CKD (**Option A**), it is unusual with the mild degree of kidney dysfunction seen in this patient. With decreasing GFR, there is an increase in fibroblast growth factor 23, which not only decreases the reabsorption of phosphorus in the renal proximal tubule but also inhibits 1-hydroxylation of vitamin D. This results in increased renal phosphorus excretion and decreased absorption of phosphorus from the gastrointestinal tract, thus maintaining serum phosphorus until late-stage CKD, at which time these homeostatic mechanisms are no longer able to counter the decrease in renal phosphorus excretion.

Because insulin stimulates the sodium-dependent phosphorus transporter, hyperphosphatemia may occur in patients with insulin deficiency (**Option B**) due to decreased cellular uptake of phosphate. However, these patients develop hyperphosphaturia and subsequent hypophosphatemia due to the effect of hyperglycosuric osmotic diuresis.

Vitamin D toxicity (**Option D**) can cause hyperphosphatemia but typically in cases of ingestion of large quantities. In addition, vitamin D–induced hyperphosphatemia is associated with elevated serum calcium levels, which are not seen in this patient.

KEY POINTS

- The cause of hyperphosphatemia can often be determined from the clinical history and is most commonly due to chronic kidney disease or acute kidney injury.
- Rhabdomyolysis and tumor lysis syndrome increase serum phosphate levels acutely due to widespread cellular damage.

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Item 85 Answer: D

Educational Objective: Diagnose renal vein thrombosis.

The most appropriate diagnostic test to perform next is renal ultrasonography with Doppler (**Option D**). This patient most likely has renal vein thrombosis (RVT), a complication of the hypercoagulable state of the nephrotic syndrome. Of the nephrotic states, RVT appears more commonly with membranous nephropathy (MN) than with other pathologies. Hematuria and flank pain are suggestive in this patient, although RVT can be asymptomatic. The gold standard diagnostic test for RVT is selective renal venography. However, less invasive procedures are more typically used. In this patient with acute kidney injury (AKI) (or an estimated glomerular filtration rate of <30 mL/min/1.73 m^2), it is preferable to avoid contrast exposure. The imaging study of first choice is ultrasonography with Doppler. If the test is negative and a high index of suspicion persists, then renal venography could be considered.

Anti–phospholipase receptor A2 antibodies (**Option A**) are present in approximately 70% of patients with MN and are emerging as a diagnostic and prognostic tool to identify and monitor disease. However, this test has no role in defining the etiology of AKI when underlying MN is known or in advancing the diagnosis of RVT.

In patients with oliguria, the fractional excretion of sodium (FE_{Na}) (**Option B**) can help distinguish between prerenal AKI and acute tubular necrosis. In prerenal AKI the FE_{Na} is <1%. However, FE_{Na} <1% can occur in other conditions, including contrast nephropathy, pigment nephropathy, glomerulonephritis, and early obstruction. FE_{Na} >2% is consistent with acute tubular necrosis. However, FE_{Na} may be >2% in patients with prerenal AKI who have urinary sodium loss due to diuretics, have adrenal insufficiency, or from bicarbonaturia in severe metabolic alkalosis. This patient is not oliguric and the presence of AKI in a patient with MN, hematuria, and flank pain strongly suggests RVT.

Although radionuclide imaging (**Option C**) may help assess if there is arterial flow to the kidney as well as estimate the glomerular filtration rate, it will not identify RVT with specificity.

KEY POINTS

- Renal vein thrombosis is a complication of the nephrotic syndrome and is most commonly associated with membranous nephropathy.
- Preferred imaging studies for suspected renal vein thrombosis in patients with acute kidney injury or an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 include renal ultrasonography with Doppler and renal venography.

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Item 86 Answer: D

Educational Objective: Manage hemodialysis line–related sepsis.

The most appropriate additional management is to remove the tunneled hemodialysis catheter (**Option D**). Infection is the second leading cause of death in patients with end-stage kidney disease (ESKD). Patients are at increased risk due to a relatively immunosuppressed state from chronic inflammation and frequent exposure to the health care environment. Tunneled dialysis catheters increase the risk for bacteremia, and empiric antibiotics should be administered while awaiting blood culture results in patients with suspected bacteremia. Tunneled catheters should be removed immediately for severe sepsis, evidence of metastatic infection, evidence of an exit-site or tunnel infection, persistent fever, or bacteremia despite administration of antibiotics.

Antibiotic lock therapy (**Option A**) consists of the instillation of a highly concentrated antibiotic solution into an intravascular catheter lumen to treat catheter-related bloodstream infections. Antibiotic lock therapy with vancomycin and/or ceftazidime is an alternative option for stable patients with less virulent organisms such as *Staphylococcus epidermitis*, but catheter salvage should not be attempted for patients with severe sepsis, *Staphylococcus aureus* infections, and some gram-negative organisms.

Arteriovenous fistula (AVF) excision (**Option B**) is not indicated. Hemodialysis arm-access sites have a lower risk for infection than do catheters; AVFs have the lowest risk compared with arteriovenous grafts. This patient has no evidence of an AVF-related infection, nor is it expected, as his AVF has not yet been used for dialysis.

Exchange of the catheter over a guidewire (**Option C**) may be an option for clinically stable patients without a tunnel infection or for patients who clear the bacteremia within 48 hours of antibiotic administration. This patient meets none of these indications for catheter exchange.

KEY POINTS

- Tunneled catheters should be removed immediately for severe sepsis, evidence of metastatic infection, evidence of an exit-site or tunnel infection, persistent fever, or bacteremia despite administration of antibiotics.
- Antibiotic lock therapy with vancomycin and/or ceftazidime is an alternative option to treat catheter-related bloodstream infections in stable patients with less virulent organisms such as *Staphylococcus epidermitis*.

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Item 87 Answer: A

Educational Objective: Diagnose Gitelman syndrome.

The most likely diagnosis is Gitelman syndrome (**Option A**), an autosomal recessive disorder that causes decreased activity in the sodium chloride transporter in the distal tubule. This patient has a hypokalemic metabolic alkalosis with a low-normal blood pressure. The differential of this presentation includes surreptitious vomiting, diuretic abuse, Bartter syndrome, and Gitelman syndrome. These patients have findings similar to those in patients being treated with thiazide diuretics. Patients with Gitelman syndrome typically present in late adolescence or early adulthood with low-normal blood pressure and hypokalemic metabolic alkalosis. Frequently, they will have hypomagnesemia and a high-normal serum calcium level. They will have low urine calcium excretion, as seen in this patient, and their urine diuretic screen will be negative. Bartter syndrome, which affects transport in the loop of Henle, has a similar presentation to Gitelman syndrome. However, Bartter syndrome typically presents in early childhood and is far less common than Gitelman syndrome. Because of significant sodium wasting, these patients will often have episodes of kidney injury due to hypotension. If measured, they typically have a normal-to-increased urine calcium.

Patients who abuse laxatives (**Option B**) typically have a low urine chloride and proportionally low sodium and potassium excretion and frequently have a normal anion gap metabolic acidosis. In this case, the urine anion gap will be positive, reflecting increase urinary excretion of hydrogen ions.

$$\text{Urine Anion Gap} = (\text{Urine Sodium} + \text{Urine Potassium}) - \text{Urine Chloride}$$

The presence of metabolic alkalosis excludes laxative abuse as the cause of hypokalemia in this patient.

Primary hyperaldosteronism (**Option C**) results from the autonomous secretion of excessive aldosterone. It is relatively common, occurring in approximately 10% of patients with hypertension. Additional signs of primary hyperaldosteronism include hypokalemia and metabolic alkalosis. The patient's low blood pressure excludes primary hyperaldosteronism as the cause of her hypokalemia and metabolic alkalosis.

Patients with surreptitious vomiting (**Option D**) will have a hypokalemic metabolic alkalosis and low-normal blood pressure similar to that seen in patients with Gitelman syndrome; however, urine chloride will be low and urine calcium excretion should not be low.

KEY POINT

- Patients with Gitelman syndrome typically present in late adolescence or early adulthood with low-normal blood pressure, hypokalemic metabolic alkalosis, and, frequently, hypomagnesemia and high-normal serum calcium levels.

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Item 88 Answer: D

Educational Objective: Prevent cardiovascular events in a patient with chronic kidney disease.

The most appropriate treatment to reduce this patient's risk of atherosclerotic cardiovascular disease (ASCVD) is moderate-intensity atorvastatin (**Option D**). The American College of Cardiology/American Heart Association Guideline on the Management of Blood Cholesterol recommends moderate-intensity statin therapy for any patient aged 40 to 75 years with diabetes mellitus. In addition, this guideline recognizes chronic kidney disease (CKD) as a risk enhancer for ASCVD and recommends a moderate-intensity statin for adults aged 40 to 75 years with an LDL cholesterol of 70 to 189 mg/dL (1.81-4.89 mmol/L) who have a 10-year ASCVD risk ≥7.5% (excluding patients treated with dialysis or kidney transplantation). The Kidney Disease: Improving Global Outcomes guidelines recommend treatment with a statin in all patients aged ≥50 years with non-dialysis-dependent CKD and in adults aged 18 to 49 years with non-dialysis-dependent CKD and any one of the following: coronary disease, diabetes, prior ischemic stroke, or a >10% estimated risk for coronary death or nonfatal myocardial infarction. The use of statins to treat dyslipidemia in patients with CKD has been shown to reduce cardiovascular events. However, statins do not slow progression of CKD. When patients reach end-stage kidney disease, statins do not reduce cardiovascular events. Atorvastatin is frequently chosen for patients with CKD because it undergoes hepatic clearance and does not require renal dose adjustments. In addition, atorvastatin may have beneficial effects on proteinuria.

There is no indication for either evolocumab or ezetimibe (**Options A, B**). The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as evolocumab, are monoclonal antibodies that bind to serine protease PCSK9, a liver enzyme that degrades hepatocyte LDL receptors. Adding a PCSK9 inhibitor can be considered for secondary prevention in very high-risk patients if the LDL cholesterol level remains ≥70 mg/dL (1.81 mmol/L) or the non-HDL cholesterol level is ≥100 mg/dL (2.59 mmol/L) despite maximally tolerated lipid-lowering therapy. Ezetimibe can be added to maximally tolerated statin therapy in very high-risk patients with clinically evident ASCVD when the LDL cholesterol level remains ≥70 mg/dL (1.81 mmol/L).

High-intensity statin therapy is not indicated in this patient, and atorvastatin is usually preferred to rosuvastatin (**Option C**), a renally excreted statin, in patients with CKD.

KEY POINTS

- The use of statins to treat dyslipidemia in patients with chronic kidney disease has been shown to reduce cardiovascular events.
- Statins do not slow progression of chronic kidney disease.

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Item 89 Answer: C

Educational Objective: Diagnose hepatitis C virus infection as the cause of membranoproliferative glomerulonephritis.

The most likely cause of this patient's glomerulonephritis is hepatitis C virus (HCV) infection (**Option C**). This patient has membranoproliferative glomerulonephritis (MPGN). Based on her history of transactional sex, she is at increased risk for HCV infection, which is a secondary cause of immune complex-mediated MPGN. If the patient tests positive for HCV, treatment of the lesion would involve anti-HCV antiviral therapy and consideration of immunosuppression (glucocorticoids plus rituximab). The approach to evaluating MPGN lesions on kidney biopsy is based on the pattern of staining on immunofluorescence microscopy. The more common pattern is immune complex deposition with both immunoglobulin (IgG, IgM, and/or IgA) and complement (C1q and/or C3) on immunofluorescence, which infers an inciting cause or event that generally falls into one of three major categories: infectious, autoimmune, or malignancy associated. The most common of these etiologies is infectious, specifically infection with HCV.

A test for genetic mutations of alternative complement pathway proteins (**Option A**) is not indicated. This extremely rare finding manifests as a MPGN lesion showing only C3 (without immunoglobulin or C1q staining) on immunofluorescence staining. This suggests an antibody-independent means of complement activation and points to hyperactivity of the alternative complement pathway. These C3 glomerulopathies, named for the isolated C3 staining pattern seen on immunofluorescence, should prompt screening for genetic abnormalities in alternative complement pathway proteins. This patient has immune complex deposition with the presence of both immunoglobulin and complement; therefore, testing for alternate pathway mutations is not indicated.

Hepatitis B virus infection and syphilis (**Options B, D**) have been linked to glomerular diseases, but these classically present with the nephrotic syndrome associated with membranous nephropathy.

KEY POINTS

- The immune complex form of membranoproliferative glomerulonephritis is associated with infectious, autoimmune, or malignancy-associated etiologies.
- The most common etiology of immune complex membranoproliferative glomerulonephritis is infectious, specifically hepatitis C virus infection.

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Item 90 Answer: C

Educational Objective: Treat hyponatremia in a symptomatic patient.

The most appropriate treatment is 3% saline plus desmopressin (**Option C**). The first step when treating symptomatic hyponatremia is determining whether it is an acute (<48 hours) or a chronic (>48 hours) presentation. For this patient with confusion, it cannot be determined how long the serum sodium level has been low; in these cases, the hyponatremia should always be treated as chronic. It is important to prevent overly rapid correction of the serum sodium. To prevent swelling, the brain cell response to hyponatremia is to extrude osmotically active solutes. This volume regulatory response occurs over 48 hours. After 48 hours, rapid increase in the serum sodium concentration will cause brain cells to acutely shrink, which can lead to osmotic demyelination syndrome (ODS). In symptomatic individuals with hyponatremia, acutely increasing the serum sodium by 3 to 4 mEq/L (3-4 mmol/L) will usually improve symptoms; if the increase in serum sodium is ≤8 mEq/L (8 mmol/L) in 24 hours, the incidence of ODS can be markedly decreased and often avoided. Because of her symptoms, it is essential to increase the serum sodium 3 to 4 mEq/L (3-4 mmol/L) quickly by administering either a 100-mL bolus or 30 mL/h of hypertonic 3% saline and measuring the serum sodium every 2 hours. However, if the hyponatremia is due to volume depletion or excessive water intake, the serum sodium can rise rapidly as the kidney excretes the excess water. Simultaneous administration of desmopressin makes the rate of correction resulting from 3% saline infusion more predictable and safer for the patient because it prevents an unexpected water diuresis and rapid increases in the serum sodium.

In symptomatic hyponatremic patients, fluid restriction (**Option A**) alone is not an appropriate treatment. The goal is to improve symptoms and prevent further neurologic complication by rapidly increasing the serum sodium level by 3 to 4 mEq/L (3-4 mmol/L) with 3% saline and desmopressin administration.

Administration of 0.9% saline (**Option B**) may lower the serum sodium in patients with the syndrome of inappropriate antidiuretic hormone secretion, because the amount of sodium infused can be excreted in a smaller volume of urine leaving behind water.

Tolvaptan (**Option D**), an antidiuretic hormone antagonist, should not be used in patients with symptomatic hyponatremia, as the response is unpredictable.

KEY POINTS

- The initial treatment of symptomatic hyponatremia is acutely increasing the serum sodium by 3 to 4 mEq/L (3-4 mmol/L) with 3% saline infusion.
- In the treatment of symptomatic hyponatremia, simultaneous administration of desmopressin with 3% saline infusion results in a more predictable and safer increase in serum sodium.

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Item 91 Answer: D

Educational Objective: Screen for albuminuria to determine optimal treatment of hypertension.

The most appropriate additional management is to obtain a urine albumin-creatinine ratio (**Option D**). Dipstick measurements of protein are dependent on urine concentration; false-negative results may be caused by dilute urine, and false-positive results may be caused by highly concentrated urine. Because moderately increased albuminuria may go undetected by dipstick urinalysis, direct quantification is required in high-risk patients. The American College of Cardiology/American Heart Association (ACC/AHA) blood pressure (BP) guideline recommends a BP goal of <130/80 mm Hg for patients with diabetes mellitus. The American Diabetes Association (ADA) recommends a BP target of <130/80 mm Hg for patients with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease [ASCVD] or 10-year ASCVD event risk ≥15%), if it can be safely attained. For patients who have diabetes and hypertension with a 10-year ASCVD <15%, the ADA recommends a target of 140/90 mm Hg. First-line therapy in non-Black patients with diabetes includes a thiazide diuretic, calcium channel blocker (CCB), ACE inhibitor, or angiotensin receptor inhibitor (ARB). First-line therapy for Black patients is a thiazide diuretic or CCB. According to the ACC/AHA, ACE inhibitors or ARBs may be considered in the presence of albuminuria. For patients with hypertension, diabetes, and urine albumin-creatinine ratio >300 mg/g, the ADA recommends an ACE inhibitor or ARB at the maximum tolerated dose as first-line treatment regardless of race or ethnicity; such treatment should also be considered if urine albumin-creatinine ratio ≥30 mg/g to 300 mg/g. Consequently, the next step in management of this patient is to measure her urine albumin-creatinine ratio to determine if an ACE inhibitor or ARB is indicated.

Selecting a specific antihypertensive drug, such as a CCB (amlodipine) (**Option A**), a thiazide diuretic (hydrochlorothiazide) (**Option B**), an ACE inhibitor, or an ARB is not indicated until quantification of albuminuria is performed.

Patients with stage 2 hypertension should be managed with both pharmacologic and nonpharmacologic therapy. Therefore, continuing nonpharmacologic therapy only is not sufficient (**Option C**). After initiation of therapy, the patient's BP should be remeasured in 1 month, not 3 months.

KEY POINTS

- Because moderately increased albuminuria may go undetected by dipstick urinalysis, direct quantification is required in high-risk patients.

(Continued)

KEY POINTS *(continued)*

- The American Diabetes Association recommends an ACE inhibitor or angiotensin receptor blocker at the maximum tolerated dose as first-line treatment for hypertension in patients with diabetes mellitus and urine albumin-creatinine ratio >300 mg/g.

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Item 92 Answer: A

Educational Objective: Diagnose alcoholic ketoacidosis.

The most likely diagnosis is alcoholic ketoacidosis (**Option A**). This patient has an increased anion gap metabolic acidosis with an anion gap of 28, and ketoacidosis due to acute ethanol intoxication is the most likely cause. Alcoholic ketoacidosis occurs in patients following an episode of acute intoxication; however, by the time of clinical evaluation, the ingested ethanol may be extensively metabolized, leading to low or absent serum ethanol levels. Ethanol is oxidized to acetaldehyde and then to acetic acid, during which process the electron-carrier coenzyme nicotinamide adenine dinucleotide (NAD+) is reduced to NADH in increasing amounts. Simultaneously, decreased insulin secretion (as a result of starvation) and increased counter-regulatory hormones cause lipolysis and generation of ketones, such as acetoacetate and β-hydroxybutyrate, which result in the anion gap. The high ratio of NADH to NAD+ leads to increased reduction of acetoacetate to β-hydroxybutyrate. Because the nitroprusside reagent in the serum and urine ketone assays detects only acetoacetate, these tests may be falsely negative due to decreased acetoacetate levels despite the presence of increased levels of the ketone β-hydroxybutyrate, as in this case. Definitive diagnosis may require direct measurement of β-hydroxybutyrate levels in the serum, which is available at some laboratories.

Ethylene glycol and methanol toxicities (**Options B, D**) are associated with a plasma osmolal gap >10 mOsm/kg H_2O. The plasma osmolal gap is calculated as the difference between the measured osmolality and calculated osmolality, which is determined as follows:

$$2 \times \text{Serum Sodium (mEq/L)} + \text{Plasma Glucose (mg/dL)}/18 + \text{Blood Urea Nitrogen (mg/dL)}/2.8$$

In this case, the difference between the calculated and measured osmolality is 3 mOsm/kg H_2O (293 mOsm/kg H_2O - 290 mOsm/kg H_2O), making either ethylene glycol or methanol toxicity unlikely.

Because isopropyl alcohol (**Option C**) is metabolized to acetone (a ketone), it will lead to ketosis but not to an acidosis. An osmolal gap, which is not present in this patient, will also develop with isopropyl alcohol intake.

KEY POINTS

- Alcoholic ketoacidosis results in an increased anion gap metabolic acidosis and minimal ketones on urine dipstick analysis.
- Ethylene glycol, methanol, and isopropyl alcohol toxicities are associated with an increased osmolal gap.

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Item 93 Answer: E

Educational Objective: Prevent recurrent calcium oxalate stone disease.

The most appropriate additional management is to start chlorthalidone (**Option E**) to decrease urinary calcium excretion to prevent recurrent calcium oxalate stones. This patient's urinary calcium excretion is in the high-normal range. The threshold that defines high urinary calcium excretion and when to initiate a thiazide diuretic for prevention of calcium oxalate stones is unclear. However, the underlying principle is that the risk for stone formation is continuous with increasing amounts of calcium in the urine. Patients with ongoing stone formation despite dietary and fluid management should be considered for medical therapy with a thiazide diuretic to decrease urinary calcium excretion. Thiazide diuretics can decrease calcium excretion by up to 50% and reduce the recurrence of calcium oxalate stones. Chlorthalidone is the preferred agent because of its long half-life. Chlorthalidone increases calcium reabsorption in the kidney primarily by causing mild volume depletion, which increases sodium and calcium reabsorption in the proximal tubule. When hydrochlorothiazide is used, twice-daily dosing is recommended. In addition to chlorthalidone, urinary calcium excretion can also be reduced by limiting sodium and protein intake.

Decreasing calcium intake (**Option A**) is not the most appropriate management. Because calcium complexes with oxalate in the gastrointestinal tract, decreasing calcium intake allows for increased oxalate absorption and increased risk for stone formation. Therefore, unless a person is on a high-calcium diet (>1500 mg/d), intake should not be limited.

There is no evidence that excess coffee intake is associated with kidney stone disease, so reduction in coffee intake (**Option B**) would not be expected to be beneficial.

Except in patients with hyperoxaluria, limiting oxalate intake (**Option C**) has not been shown to decrease the incidence of stones, and thus the patient does not need to decrease intake.

Because uric acid may serve as a nidus for stone formation, allopurinol (**Option D**) has been used to reduce stone occurrence, especially in patients with high levels of uric acid in the urine, which is not present in this patient.

KEY POINTS

- Thiazide diuretics decrease calcium excretion by up to 50% and can be used to manage recurrent calcium oxalate kidney stones.
- In patients with recurrent calcium oxalate kidney stones, urinary calcium excretion can be reduced by limiting sodium and protein intake.

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Item 94 Answer: C

Educational Objective: Manage end-stage kidney disease with non-dialytic palliative therapy.

The most appropriate management is to intensify hypertension management (**Option C**). Treatment options for patients with end-stage kidney disease (ESKD) include dialysis, transplantation, and the less aggressive option of non-dialytic medical management only. Shared decision-making is vital with these patients. This patient reached an informed decision to pursue non-dialytic medical management. This management is particularly appropriate for older patients with ESKD and comorbid conditions who may gain only minimal, if any, additional lifespan. Non-dialytic medical therapy avoids the burdens of dialysis and is associated with fewer hospitalizations compared with older patients who initiate hemodialysis. The goal of medical management is to prolong the comfort and functioning of a patient's life through ongoing medical management of medical problems. The appropriate intervention for this patient is to intensify her hypertension management, as she has a history of stroke and her blood pressure is 160/72 mm Hg. Blood pressure recommendations differ for older patients, but reduction of systolic blood pressure to <140 mm Hg in patients with stroke is generally supported.

Adding a phosphate binder (**Option A**) is not appropriate management, as her serum phosphorus level is in the normal range.

Discontinuing all medications other than insulin (**Option B**) in not compatible with the philosophy of non-dialytic medical management, which includes ongoing medical management of medical problems.

This patient functions well in her life and has no particular needs that will be met with hospice care. Hospice referral (**Option D**) may be indicated in the future as her chronic kidney disease progresses.

KEY POINT

- The goal of non-dialytic palliative therapy in patients with end-stage kidney disease involves ongoing medical management of medical problems to prolong comfort and functioning.

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Item 95 Answer: A

Educational Objective: Screen for urothelial cancer in a patient with hematuria and aristolochic acid nephropathy.

Cystoscopy with retrograde pyelography (**Option A**) is the most appropriate management for this patient to assess for evidence of urothelial tumor. Chronic tubulointerstitial nephritis (CTIN) in the setting of protracted use of herbal medications, particularly those of Chinese origin, suggests the possibility of aristolochic acid nephropathy. Consequently, this patient may be at increased risk for urothelial cancer despite her young age. CT of the abdomen and pelvis is not sufficiently sensitive to rule out neoplasia of the ureters or bladder.

MRI of the kidneys (**Option B**) is not the most appropriate test for evaluating the lower urinary tract. Although an MRI may be ordered as an alternative imaging modality in evaluating for renal masses, CT remains the gold standard.

Renal angiography (**Option C**) may be considered for persistent gross hematuria of uncertain etiology when all other lower urinary tract imaging modalities have failed to identify a cause, but it would not be the most appropriate management in this case.

In a young patient without risk factors for urothelial cancer (such as smoking, occupational exposure, use of Chinese herbal medications), exclusion of stone, renal mass, and active urinary tract infections followed by expectant observation (**Option D**) is appropriate for a single episode of gross hematuria. This patient's analgesic use is relatively low to ascribe the CTIN to this etiology with confidence. There is no history of occupational or other environmental exposure, and there is no test available to identify aristolochic acid as the cause of this patient's CTIN. However, given the patient's history of protracted use of herbal medications, it would be prudent to rule out the associated risks of herbal medication use, such as urothelial tumor.

KEY POINTS

- Certain Chinese herbal medications have been associated with aristolochic acid nephropathy, which can cause chronic tubulointerstitial disease and is associated with urothelial cancer.
- CT urography and cystoscopy with retrograde pyelography are the most appropriate tests for a patient with hematuria and risk factors for urothelial cancer.

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Item 96 Answer: C

Educational Objective: Treat infection-related glomerulonephritis.

Continuing nafcillin (**Option C**) is the most appropriate treatment for this patient with infection-related glomerulonephritis (IRGN). IRGN results from a recently resolved infection or an ongoing infection at the time of development of glomerulonephritis. Diabetes mellitus is the most common comorbidity, and older age (>65 years) is a key risk factor; both factors are present in this patient. Treatment of IRGN is typically supportive and aimed at the infectious etiology.

The prognosis for complete recovery from IRGN is excellent in children. However, in adults, the prognosis of the newly recognized forms of IRGN (e.g., due to *Staphylococcus aureus* and gram-negative organisms) is less favorable, with more patients developing severe kidney dysfunction, progressing to chronic kidney disease (CKD) and sometimes to end-stage kidney disease. Initiation of an ACE inhibitor such as lisinopril (**Option A**) at the time of acute kidney injury is not recommended. However, in this patient's long-term follow-up, lisinopril therapy is a reasonable option if he develops proteinuric CKD as a residual of IRGN.

Adding a trial of glucocorticoid therapy such as prednisone (**Option B**) to antibiotic therapy for IRGN is considered only in rare cases in which a severe proliferative glomerulonephritis on biopsy is accompanied by a rapid progression toward kidney failure. In this patient, the glomerular lesion is not described as severe, and his serum creatinine levels during his hospitalization do not indicate rapidly progressive glomerulonephritis defined by at least a 50% decline in glomerular filtration rate over a short time period.

The indication for diuretics and sodium restriction is the presence of hypertension and edema secondary to fluid retention. In these cases, sodium restriction and a loop diuretic (**Option D**) are recommended first-line therapies. Because this patient does not have evidence of hypertension or edema, these therapies are not indicated.

KEY POINT

- Treatment of infection-related glomerulonephritis is typically supportive and aimed at the infectious etiology.

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Item 97 Answer: D

Educational Objective: Diagnose preeclampsia.

The most likely diagnosis is preeclampsia (**Option D**). Preeclampsia is defined as new-onset hypertension with proteinuria (≥300 mg/24 h or a urine protein-creatinine ratio ≥300 mg/g) after 20 weeks of pregnancy. Preeclampsia can also be diagnosed in patients without proteinuria if the hypertension is accompanied by evidence of other end-organ damage. End-organ involvement that meet the diagnostic criteria for preeclampsia includes thrombocytopenia (platelet count <100,000/μL [100 × 10^9/L]); kidney dysfunction (serum creatinine >1.1 mg/dL [97.2 μmol/L]) or a doubling of the serum creatinine concentration); impaired liver function (elevated aminotransaminases levels to ≥2 times the upper limit of normal); pulmonary edema; and cerebral or visual symptoms such new-onset headache unresponsive to medication and not accounted for by alternative diagnoses. In this patient, hypertension, kidney dysfunction, and new-onset headache are present.

Acute fatty liver of pregnancy (AFP) (**Option A**) is a rare but serious condition that also occurs late in pregnancy. It presents with symptoms similar to those of HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Indicators of liver failure, including hypoglycemia and coagulopathy, are often worse in AFP than in HELLP syndrome. This patient has no manifestations of AFP.

International Headache Society criteria for migraine (**Option B**) without aura include at least five headache attacks lasting 4 to 72 hours; at least four migraine characteristics (unilateral location, pulsating quality, inhibits or prohibits daily activities, aggravation by walking up or down stairs or similar routine physical activity); and at least one associated symptom (nausea/vomiting, photophobia/phonophobia). In addition, the headache cannot be better accounted for by another diagnosis. Preeclampsia is a better explanation for this patient's headache.

Hypertension associated with pheochromocytoma (**Option C**) can show a sustained pattern, with or without paroxysms, or occur as paroxysms only. Pheochromocytoma is rare and typically associated with additional findings (tachycardia, nervousness, diaphoresis). Proteinuria and acute elevation of serum creatinine are not typical manifestations.

KEY POINTS

- Preeclampsia is defined as new-onset hypertension with proteinuria (≥300 mg/24 h or a urine protein-creatinine ratio ≥300 mg/g) after 20 weeks of pregnancy.
- Preeclampsia can be diagnosed in pregnant patients without proteinuria if hypertension is accompanied by evidence of other end-organ damage (thrombocytopenia, kidney dysfunction, liver dysfunction, pulmonary edema, cerebral or visual symptoms).

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Item 98 Answer: D

Educational Objective: Evaluate kidney function with serum cystatin C measurement.

The most appropriate test is serum cystatin C measurement (**Option D**). Reduction of muscle mass, as seen in amputees and those with malnutrition or muscle wasting, can result in

a lower serum creatinine concentration without a change in glomerular filtration rate (GFR). Because of decreased muscle mass, serum creatinine overestimates kidney function in older persons, especially women. Young persons and men often have higher muscle mass and higher serum creatinine concentration at a given GFR compared with older persons and thus underestimates kidney function in this population. This patient's elevated serum creatinine level is likely the result of increased muscle mass. Serum cystatin C is an alternative marker of GFR that is less influenced than serum creatinine by age, sex, muscle mass, and body weight. Cystatin C is produced by all nucleated cells, completely filtered by glomeruli, and then metabolized by renal tubules; serum levels thus provide an index of GFR. Serum cystatin C is more sensitive in identifying milder decrements in kidney function than serum creatinine.

Blood urea nitrogen (BUN) (**Option A**) is derived from the metabolism of proteins. BUN concentration is a poor marker of kidney function because it is not produced at a constant rate and is reabsorbed along the tubules; furthermore, alterations in renal blood flow markedly influence tubular reabsorption and excretion.

Because of the secretion of creatinine in the proximal tubule, the direct measurement of creatinine clearance (**Option B**) with a 24-hour urine collection tends to overestimate GFR. Nonetheless, with an adequate collection, the 24-hour urine collection can be used to estimate GFR; however, this test is prone to collection errors and would be unnecessarily burdensome for this patient.

Radionuclide imaging (**Option C**) provides the most accurate measurement of GFR and is the gold standard in research. It is useful for accurate determination of GFR during evaluation of kidney donors, evaluation of recipients for other organs, or assessment of the differential GFR of each kidney before nephrectomy. However, for this patient, the availability of serum cystatin C measurement makes radionuclide imaging unnecessary.

KEY POINTS

- Increased or decreased muscle mass can alter the serum creatinine level in the absence of kidney disease.
- Serum cystatin C is more sensitive in identifying milder decrements in kidney function than serum creatinine.

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Item 99 Answer: D

Educational Objective: Diagnose renal AL amyloidosis.

Renal AL amyloidosis (**Option D**) is the most likely diagnosis in this patient. Amyloidosis is characterized by extracellular tissue deposition of fibrillary protein. The gold standard for pathologic diagnosis is the characteristic apple-green birefringence with Congo red stain when kidney biopsy specimens are examined under polarized light. The most common form of renal amyloidosis, occurring in 60% to 65% of patients, is derived from monoclonal immunoglobulin light chains (AL amyloid, as in this case). Amyloidosis may be confined to one organ or affect multiple organs; kidney involvement is common in systemic amyloidosis. AL amyloidosis typically affects patients >50 years of age, predominantly men. When kidney involvement occurs, patients typically present with nephrotic-range proteinuria (with the full nephrotic syndrome seen in 25% to 50% of patients) as well as some degree of renal insufficiency. Serum and urine protein electrophoresis with immunofixation can identify the monoclonal protein, but quantification of serum free light chains (κ, λ) provides a more sensitive assay. In practice, all three testing modalities are usually checked simultaneously.

Diabetic kidney disease (**Option A**) typically occurs after long-standing type 2 diabetes mellitus (typically >10 years' duration) in patients with other evidence of microvascular or macrovascular complications of disease, most notably diabetic retinopathy, which this patient did not have. In the absence of these characteristic findings, a kidney biopsy should be performed to establish a diagnosis.

IgA nephropathy (IgAN) (**Option B**) is the most common primary glomerular disease worldwide, usually diagnosed in youth or early adulthood. IgAN can present with any of the manifestations of the nephritic syndrome. Diagnosis may be suspected clinically but can only be made by kidney biopsy showing dominant mesangial immune deposits of IgA with C3, and occasionally IgG or IgM. This older patient presenting with the nephrotic syndrome is not compatible with the diagnosis of IgAN.

Patients with membranous nephropathy (**Option C**) typically describe slowly progressive edema, and laboratory testing reveals proteinuria, hypoalbuminemia, and hyperlipidemia, most often with preserved kidney function. Diagnosis is traditionally made by kidney biopsy, although serologic testing for anti-phospholipase A2 receptor antibodies allows for the possibility of diagnosing the disease noninvasively. The hallmark biopsy finding is the presence of subepithelial immune deposits.

KEY POINT

- The gold standard for pathologic diagnosis of amyloidosis is the characteristic apple-green birefringence with Congo red stain when examined under polarized light.

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Item 100 Answer: D

Educational Objective: Diagnose minimal change glomerulopathy with acute kidney injury.

The most likely diagnosis is minimal change glomerulopathy (MCG; also known as minimal change disease) (**Option D**) in

this older patient who has the nephrotic syndrome with acute kidney injury (AKI). MCG is the most common cause of the nephrotic syndrome in children (>90% of cases), but it is also responsible for 10% to 15% of cases of the nephrotic syndrome in adults, especially older patients (≥65 years of age) and elderly patients (≥80 years of age). The classic presentation of MCG is sudden-onset nephrotic syndrome with abrupt appearance of edema and, eventually, anasarca. Up to 25% of adults with MCG may also have AKI, with an increased risk in older patients with hypertension, low serum albumin levels, and heavy proteinuria. Another cause of the nephrotic syndrome with AKI includes MCG with concomitant interstitial nephritis in the setting of NSAID use and collapsing forms of focal segmental glomerulosclerosis.

Both ANCA-associated glomerulonephritis and anti-glomerular basement membrane antibody disease (**Options A, B**) can cause severe AKI in an elderly patient, but the urinary findings in these rapidly progressive glomerulonephritides show both hematuria and subnephrotic-range proteinuria. This patient's findings on urinalysis are typical of the nephrotic syndrome, not glomerulonephritis.

Membranous nephropathy (**Option C**) can also cause the nephrotic syndrome and AKI. However, AKI seen in membranous nephropathy is usually due to renal vein thrombosis, which was not seen on this patient's Doppler ultrasound. Membranous nephropathy is most commonly diagnosed in middle-aged adults, with a slight male predominance, and is an unusual etiology of the nephrotic syndrome in patients >75 years of age unless there is an underlying malignancy. Furthermore, the onset of edema in membranous nephropathy is usually slower than in MCG.

KEY POINTS

- The classic presentation of minimal change glomerulopathy is sudden-onset nephrotic syndrome with abrupt appearance of edema and, eventually, anasarca.
- Up to 25% of adults with minimal change glomerulopathy may have acute kidney injury, with a particular risk in older patients with hypertension, low serum albumin levels, and heavy proteinuria.

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Item 101 Answer: A

Educational Objective: Manage end-stage kidney disease.

The most appropriate next step in management is to discuss goals of care (**Option A**). This patient has end-stage kidney disease (ESKD) due to long-standing urinary retention from prostatic hyperplasia. There is no significant diuresis during the 48 hours since bladder catheter placement, and the decrease in his serum creatinine level is insignificant. The small kidney sizes with severe cortical echogenicity and thinning suggest advanced chronic kidney disease. Patients with ESKD and advanced age or multiple comorbidities may not want renal replacement therapy. For these patients, palliative care aimed at improving the quality of life may be a better option. Such care aligns treatment with a patient's goals through culturally sensitive shared decision-making and advance care planning, along with treating symptoms resulting from uremia, hypervolemia, hyperkalemia, and/or acidosis. Therefore, a discussion of overall goals of care is the most appropriate next step.

Initiating intravenous 0.9% saline (**Option B**) is not an appropriate management step. The patient does not appear hypovolemic, and volume expansion will not help.

In patients with obstructive uropathy, noncontrast CT of the abdomen and pelvis (**Option C**) is indicated for suspected nephrolithiasis. The patient's finding of persistent hydronephrosis on repeat kidney ultrasound is not unusual in patients a few days following relief of long-standing obstruction and does not indicate the presence of bilateral ureteral obstruction. Similarly, there is no indication that ureteral stents will further improve kidney function (**Option D**).

KEY POINTS

- Long-standing obstructive uropathy may lead to end-stage kidney disease even if the source of obstruction is corrected.
- Patients with end-stage kidney disease and advanced age or multiple comorbidities may not want renal replacement therapy and will benefit from a discussion focused on overall goals of care.

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Item 102 Answer: D

Educational Objective: Treat autosomal dominant polycystic kidney disease with tolvaptan.

The most appropriate treatment for this patient is tolvaptan (**Option D**). In 2018, tolvaptan was approved by the FDA to slow kidney function decline in adults at risk for progressive autosomal dominant polycystic kidney disease (ADPKD). This patient has four known risk factors associated with progression to end-stage kidney disease (ESKD): onset of hypertension before 35 years of age; urologic events (gross hematuria, cyst infection, and/or flank pain) before 35 years of age; an estimated glomerular filtration rate decrease >5 mL/min/1.73 m^2 within 1 year; and a family history of ESKD at or before 58 years of age. Other risk factors associated with progression to ESKD include male sex, total kidney volume greater than expected for age, and truncating *PKD1* variant.

Before the availability of tolvaptan, blood pressure control using blockade of the renin-aldosterone system was the only validated therapeutic strategy for management of ADPKD. This conservative therapy should still be a staple of

treating patients with ADPKD, including those on tolvaptan. This patient is already taking an ACE inhibitor with blood pressure at goal; she would not be expected to have any benefit from switching to an angiotensin receptor blocker such as telmisartan at this point (**Option A**).

Measurement of total kidney volume can be important in assessing risk for ESKD in patients with ADPKD; volume can be compared to expected volume for age, and changes in volume over time can also be assessed. Ultrasonography (**Option B**) is an acceptable modality for kidney size and cyst burden but is inferior to MRI for measurement of total kidney volume. This patient, however, does not require a measurement of total kidney volume to be considered high risk given her confluence of other risk factors; she can proceed directly to tolvaptan therapy without a kidney volume measurement.

Octreotide (**Option C**) has been shown to reduce kidney cyst fluid accumulation in selected patients with ADPKD but has not been shown to slow the decline in kidney function as seen with tolvaptan.

KEY POINTS

- Tolvaptan can slow kidney function decline in adults at risk for progressive autosomal dominant polycystic kidney disease.
- Blockade of the renin-aldosterone system is a staple of treating patients with autosomal dominant polycystic kidney disease, including those on tolvaptan.

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Item 103 Answer: A

Educational Objective: Diagnose primary hyperaldosteronism as a secondary cause of hypertension.

The most appropriate diagnostic test to perform next is the plasma aldosterone concentration/plasma renin activity ratio (**Option A**). Primary hyperaldosteronism, in which aldosterone production cannot be suppressed with sodium loading, is the most common cause of secondary hypertension in middle-aged adults and an important cause of resistant hypertension. A triad of resistant hypertension, metabolic alkalosis, and hypokalemia (including in patients treated with low-dose thiazide diuretics) should raise suspicion. Screening is recommended if any of the following are present: resistant hypertension; hypokalemia (spontaneous or substantial, if diuretic induced); incidentally discovered adrenal mass; family history of early-onset hypertension; moderately severe hypertension (>160/100 mm Hg); or stroke at age <40 years. It is common for patients with primary hyperaldosteronism to have normal serum potassium levels; a high index of suspicion is therefore required. This patient has substantial hypokalemia (serum potassium level of 2.9 mEq/L [2.9 mmol/L]) with initiation of low-dose hydrochlorothiazide and persistent, moderately severe hypertension. The patient also has a metabolic alkalosis.

Plasma fractionated metanephrines (**Option B**) are obtained to screen for a pheochromocytoma. The absence of episodic palpitations, headaches, and tachycardia and the presence of metabolic alkalosis and hypokalemia make pheochromocytoma a less likely diagnosis for this patient.

Renal artery CT angiography (**Option C**) is an appropriate screening test for renovascular disease, including fibromuscular dysplasia. Older patients with renovascular hypertension often have other manifestations of atherosclerosis, including the presence of coronary artery, cerebrovascular, or peripheral vascular disease. Lateralizing abdominal bruits may be auscultated. Abrupt onset of hypertension in patients <35 years of age suggests fibromuscular dysplasia. None of these clinical findings is present to suggest the diagnosis of renovascular disease.

The 24-hour urine free cortisol (**Option D**) is a frequently used screening test for hypercortisolism. In adults, hypercortisolism may manifest as hypertension and hypokalemia, but it is relatively rare compared with primary hyperaldosteronism. In the absence of Cushingoid facies, central obesity, proximal muscle weakness, and ecchymosis, Cushing syndrome is a very unlikely cause of this patient's hypertension.

KEY POINTS

- Primary hyperaldosteronism is the most common cause of secondary hypertension and should be suspected in patients with resistant hypertension, hypokalemia, family history of early-onset hypertension, blood pressure >160/100 mm Hg, or stroke at age <40 years.
- The plasma aldosterone concentration/plasma renin activity ratio is the recommended screening test for primary hyperaldosteronism.

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Item 104 Answer: A

Educational Objective: Manage edema associated with the nephrotic syndrome.

The most appropriate management is to add metolazone (**Option A**). This patient with the nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS) has refractory edema despite therapy with maximal doses of oral furosemide and therefore needs additional diuretic therapy. Addition of a second diuretic that works distal to the loop of Henle, such as a thiazide diuretic and/or a potassium-sparing diuretic, is the appropriate next step in management. In patients taking high-dose loop diuretics, increased delivery of salt and water to the distal portions of the nephron can lead to hypertrophy of these segments and overabsorption of sodium, undermining the effects of the loop diuretic.

Factors that warrant admission for intravenous (IV) diuretics include lack of response after addition of a thiazide and/or potassium-sparing diuretic to a loop diuretic; acute respiratory symptoms secondary to pulmonary edema; or significant ascites that raise concern for gut edema and malabsorption of oral diuretics. These factors are not present in this patient. A number of randomized clinical trials have evaluated the efficacy of a continuous IV infusion of loop diuretics compared with IV bolus therapy (**Options B, C**). Findings indicated that continuous IV infusion is associated with less ototoxicity than bolus injections of loop diuretics, but clear evidence of its diuretic superiority is lacking, at the minimum in heart failure patients.

This patient's significant edema alongside persistent nephrotic-range proteinuria and hypoalbuminemia does not warrant discontinuation of prednisone (first-line therapy for FSGS) for the addition of cyclosporine (second-line therapy for FSGS) (**Option D**), as the patient has received glucocorticoid therapy for only 3 weeks. In adults with FSGS, therapeutic response can take up to 12 to 16 weeks. Therefore, it would be premature to consider this patient refractory to glucocorticoid therapy.

Hemodialysis with ultrafiltration (**Option E**) for edema is reserved for patients with anasarca, significant kidney dysfunction, and an inability to diurese on maximal doses of IV diuretics.

KEY POINT

- In patients with the nephrotic syndrome and refractory edema despite high-dose loop diuretics, adding a thiazide diuretic and/or a potassium-sparing diuretic is the appropriate next step in management.

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Item 105 Answer: D

Educational Objective: Diagnose crystal-induced acute kidney injury in patients receiving intravenous acyclovir.

The most likely cause of this patient's acute kidney injury (AKI) is intratubular obstruction (**Option D**). Intratubular obstruction can cause AKI through precipitation of crystals within the tubular lumen. Urinary findings include hematuria, pyuria, and crystals. This patient received intravenous high-dose acyclovir, which can cause acute AKI due to intratubular obstruction from acyclovir crystal precipitation. Predisposing factors for crystal-induced AKI include chronic kidney disease and volume depletion. Aggressive volume expansion is recommended during high-dose acyclovir therapy for these patients. Correction of volume depletion is also critical for the treatment of crystal-induced AKI as well as discontinuation of the drug if possible.

Acute glomerulonephritis (**Option A**) is not a likely cause of this patient's AKI. This patient has hereditary nephritis, which can lead to chronic glomerular basement membrane changes but not acute glomerulonephritis. Furthermore, neither acute viral encephalitis nor acyclovir is associated with acute glomerulonephritis.

Acute interstitial nephritis (AIN) (**Option B**) is a common cause of AKI and is characterized by inflammation and edema of the interstitium. The classic clinical presentation of fever, rash, and peripheral eosinophilia occurs in only 10% to 30% of patients with AIN. Drug-induced AIN, especially due to antibiotics, is the most common cause of AIN and should be considered in any patient with AKI, a characteristic urinalysis, and history of any drug exposure. Drug-induced AIN typically takes 7 to 10 days to develop and is characterized by substantial pyuria and leukocyte casts, which is not seen in this patient's urinalysis results.

Acute tubular necrosis (**Option C**) is usually suggested by urine sediment that shows pigmented brown casts and debris, which are not seen in this patient's urinalysis results.

KEY POINTS

- Intravenous acyclovir can cause acute kidney injury due to intratubular obstruction from acyclovir crystal precipitation.
- Correction of volume depletion is critical for the prevention and treatment of crystal-induced acute kidney injury.

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Item 106 Answer: B

Educational Objective: Treat hyperkalemia.

The most appropriate management is to add patiromer (**Option B**), a potassium binder, to treat this patient's moderate hyperkalemia. Initial evaluation of hyperkalemia requires a review of all medications, assessment of kidney function, and an ECG. Initial ECG manifestations include peaked precordial T waves and a shortened QT interval. Hyperkalemia frequently occurs in chronic kidney disease with an estimated glomerular filtration rate <20 mL/min/1.73 m^2. Hypoaldosteronism caused by inhibitors of the renin-angiotensin system, heparin, type 4 (hyperkalemic distal) renal tubular acidosis, or primary adrenal insufficiency also cause hyperkalemia. All potentially causative medications should be discontinued if possible. Although angiotensin receptor blockers (ARBs) such as losartan frequently cause hyperkalemia by decreasing aldosterone levels, guidelines recommend their use to slow the progression of kidney disease and provide cardiovascular protection. This patient has severely increased albuminuria, which puts her at increased risk for both progressing to end-stage kidney disease and a cardiovascular event. Routine discontinuation of ARBs has been associated with worsening outcomes; with the addition of effective potassium binders, discontinuation of ARBs is discouraged. Therefore, because

of the beneficial cardiovascular and renal effects of blocking angiotensin, if serum potassium is only mildly elevated (as in this patient), the use of potassium binders may allow the patient to continue use of losartan. Patiromer and sodium zirconium cyclosilicate are two FDA-approved potassium binders. The choice of binder is determined by patient and physician preference, as each agent has its advantages and disadvantages. Sodium polystyrene sulfonate is no longer recommended as a potassium binder due to its poor efficacy in lowering potassium and numerous reported adverse effects.

Adding a thiazide diuretic such as hydrochlorothiazide (**Option A**) may improve this patient's hyperkalemia. However, it could result in volume depletion with decreased delivery of sodium to the potassium secretory sites, resulting in worsening hyperkalemia. In addition, this patient's blood pressure is at goal and there is no indication to further lower it.

When hyperkalemia is associated with changes on ECG, intravenous calcium gluconate (**Option C**) should be administered to stabilize the cardiac membrane by raising threshold potential. Because this patient's serum potassium was only moderately elevated and her ECG was normal, calcium gluconate is not indicated.

Providing this patient with no treatment is inappropriate (**Option D**). Although her serum potassium is only moderately elevated, serum potassium levels >5 mEq/L (5 mmol/L) are associated with increased morbidity and mortality.

KEY POINTS

- Potassium binders such as patiromer and sodium zirconium cyclosilicate can be used to treat hyperkalemia in patients with chronic kidney disease.
- Use of potassium binders in patients with chronic kidney disease may allow continuation of essential medications, such as inhibitors of the renin-angiotensin system.

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Item 107 Answer: B

Educational Objective: Discontinue mycophenolate mofetil in a patient who is planning pregnancy.

Mycophenolate mofetil (**Option B**) should be discontinued in this patient before conception. Before discontinuation of mycophenolate and attempted conception, steps should be taken to ensure disease stability in this patient. Pregnancy planning is essential for ensuring positive outcomes and includes adjusting medications and optimizing clinical status. This patient is taking mycophenolate mofetil, a teratogenic agent that is contraindicated in pregnancy. Documented risks with mycophenolate mofetil use include first-trimester pregnancy loss and fetal malformations of the distal limbs, heart, esophagus, kidneys, and cleft lip and palate. Mycophenolate mofetil is also contraindicated in women who are breastfeeding because the drug is excreted into breast milk. This patient should discontinue this agent and, if continued immunosuppression is required, be switched to azathioprine, which is generally safer and well tolerated in pregnancy. In diseases such as systemic lupus erythematosus (SLE) in which mycophenolate mofetil is commonly used, patients should show stable disease for 3 to 6 months following discontinuation of the agent before proceeding with pregnancy.

Hydroxychloroquine (**Option A**) has been used safely in pregnancy. This patient who is planning a pregnancy would be recommended to continue taking this drug. Hydroxychloroquine is initiated in every patient with SLE who can tolerate it, because evidence suggests it reduces disease-associated damage, prevents disease flares, and improves kidney and overall survival. In addition, hydroxychloroquine may reduce the risk for thrombosis, liver disease, and myocardial infarction; improve lipid profiles; and improve outcomes in high-risk pregnancies.

Glucocorticoids such as prednisone (**Option C**) increase the risk for pregnancy-induced hypertension and diabetes mellitus but can be continued during pregnancy when the benefits outweigh the risks to the patient and fetus. Steps can be taken to reduce the risk of glucocorticoid therapy during pregnancy, including using the lowest dose possible for the shortest period of time; carefully managing preexisting medical conditions that may be exacerbated by glucocorticoid therapy (for example, osteoporosis, diabetes, and hypertension); and carefully monitoring for treatment adverse effects and providing early intervention should they arise.

Making no changes to this patient's medication regimen (**Option D**) would not be appropriate because mycophenolate mofetil is teratogenic and is contraindicated during pregnancy.

KEY POINTS

- Mycophenolate mofetil is teratogenic and is contraindicated in pregnancy.
- In diseases in which mycophenolate mofetil is used, patients should show stable disease for 3 to 6 months following discontinuation of the agent before proceeding with pregnancy.

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Item 108 Answer: A

Educational Objective: Treat a patient with diabetic kidney disease using a sodium-glucose cotransporter 2 inhibitor.

The most appropriate treatment is to add canagliflozin (**Option A**). There are a limited number of interventions

proven to slow the decline of kidney function in patients with chronic kidney disease (CKD). Proven interventions include glycemic control, blood pressure control, renin-angiotensin system (RAS) blockers, and avoidance of renal toxins. For patients with diabetic kidney disease, the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors slows the progression of CKD and reduces the risk for death from kidney or cardiovascular complications. For this patient with stage G3 CKD with nephrotic-range proteinuria due to type 2 diabetes mellitus, the SGLT2 inhibitor canagliflozin should be added to her medication regimen. Glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide are also suggested by the American Diabetes Association because they reduce the risks for cardiovascular events and hypoglycemia and appear to possibly slow CKD progression.

Glyburide (**Option B**) is a second-generation sulfonylurea; pioglitazone (**Option D**) is a thiazolidinedione; and sitagliptin (**Option E**) is a dipeptidyl peptidase 4 inhibitor. Drugs from these classes have a neutral effect on the progression of CKD. The use of glyburide in patients with CKD is generally avoided because of the risk for hypoglycemia. Thiazolidinediones are used with caution in patients with CKD due to the potential for fluid retention.

Adding losartan (**Option C**), an angiotensin receptor blocker (ARB), is contraindicated for this patient, as she is currently receiving lisinopril, an ACE inhibitor. Blockade of the RAS has been shown to slow the rate of progression for proteinuric CKD and is indicated for all patients who can tolerate this medication class. However, dual blockade with an ACE inhibitor and an ARB results in more adverse events without additional kidney benefit.

KEY POINTS

- Sodium-glucose cotransporter 2 inhibitors slow the progression of chronic kidney disease and reduce the risk for death from kidney or cardiovascular complications in patients with diabetic kidney disease.
- Glucagon-like peptide-1 receptor agonists reduce the risks for cardiovascular events and hypoglycemia and appear to possibly slow chronic kidney disease progression.

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